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Replication of a computer model of auditory hallucinations in schizophrenia

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Introduction. Abnormal synaptic pruning has been proposed by some authors as a theory to explain schizophrenia. It has been studied in different ways, some of which are computerized models.

Methods. A PC computer with MATLAB version 5.3 and Neural Networks Toolbox programs were used. To reproduce the model we used Elman's network for neuronal unit and McGlashan and Hoffman's network.

Results. The corrected percentage of detection improved as synapses were prunned. It increased from 68 % to 91 %, reaching the highest detection level when 60 % of the synapses were eliminated. Detection capacity was reduced when synaptic elimination continued and the program started detecting words in the absence of input. This was considered as a hallucination. When pruning reached from 80 % to 95 %, hallucinations occurred more frequently.

Conclusions. The computer simulation model provides a symptom formation model, and also a way of understanding pruning's adaptative utility. When the neuronal units were eliminated (instead of connections), there was only progressive worsening in word perception. This confirms the hypothesis proposed that schizophrenia pathophysiology underlies neuronal connections, not the neurons.

Key words:
Schizophrenia. Pruning. Computer model.

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Reproducción de un modelo informático de las alucinaciones auditivas en la esquizofrenia

Introducción. El podado sináptico anormal ha sido propuesto por algunos autores como una teoría para explicar a la esquizofrenia y ha sido estudiado de diversas maneras. Entre las aproximaciones al estudio de este fenómeno se ha utilizado la simulación computacional.

Método. Se utilizó un ordenador PC y los programas computacionales MATLAB versión 5.3 y Neural Networks Toolbox. Para la reproducción del modelo se utilizó la red de Elman para la unidad neuronal y la red publicada por McGlashan y Hoffman.

Resultados. A medida que se eliminaron las sinapsis el porcentaje correcto de detección aumentó del 68 al 91 %, llegando a la cima cuando hubo una eliminación aproximada del 60 %. Cuando se continuó con la eliminación disminuyó la capacidad de detección y se presentaron palabras en la ausencia de una entrada, lo cual se consideró como una alucinación. Éstas se presentaron con mayor frecuencia cuando el podado alcanzó entre el 80 y 95 %.

Conclusiones. El modelo de simulación por ordenador no sólo provee un modelo para la formación de síntomas, sino que también un entendimiento de la utilidad adaptativa del podado. Cuando las unidades neuronales, en vez de las conexiones, fueron eliminadas sólo se obtuvo un empeoramiento progresivo de la percepción, esto confirma la hipótesis propuesta de que la fisiopatología de la esquizofrenia subyace en la conexión entre las neuronas y no en las neuronas mismas.

Palabras clave:
Esquizofrenia. Podado. Modelo informático.

INTRODUCTION

Some investigators have proposed that schizophrenia is a neurodevelopment disorder[1-3]. In *post mortem* studies of the middle frontal cortex in humans, it has been observed that normal postnatal development is characterized by overelaboration of neuronal processes (synaptogenesis), followed by a gradual reduction of synaptic density by close to 60 % of the maximum levels in adult life[4]. In the human being, this process is completed in the occipital cortex and in the prefrontal areas at about 2 years and it finishes around adolescence in the association areas[5]. This symptogenesis is performed randomly during development with a subsequent selective elimination of the weakest connections based on experience and endogenous factors, a process that is known as pruning[6].

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Pruning outstanding during normal adolescence suggests that schizophrenia could arise as a pathological extension of this development process[1,3] and agrees with the characteristic age of onset of schizophrenia that is between late adolescence and early adulthood, which supports the theory of an alteration in neurodevelopment. Mechanisms of normal neuronal elimination and elimination in schizophrenia are unknown but could reflect overactivation («exitotoxicity») or poor neuronal usage[2,7].

The studies indicate that the disease symptoms arise in the neurocircuit used for perceptual speech processing. It has been suggested that alterations in sensory gating or habituation, which represents the simplest form of learning and is defined as decrease in response after repetition of an initial stimulus[8], are associated with the development of schizophrenia symptoms[9]. Sensory gating is conceived as the skill to discriminate trivial stimuli. Theoretically, patients with schizophrenia have a defect in the gating mechanism that results in a sensorial overload with the consequent cognitive fragmenting[10].

Theoretically, alterations in habituation reflect incapacity to eliminate the result to a repeated stimulus. Studies with auditory and tactile evoked potentials suggest an alteration in habituation in schizophrenic patients[11].

Because the spoken language is a characteristic of the human being, it is the only animal on earth that suffers schizophrenia[12]. That is why it has been proposed that schizophrenia is, in some way, the «price» that the Homo sapiens has to pay in the evolution to access language[13].

Hallucinations commonly consist in spoken language or «voices», a phenomenological characteristic that suggests that hallucinatory language involves neuronal systems dedicated to the perception of auditory speech. This has been supported by neuroimaging studies, both positron emission tomography and functional magnetic resonance imaging (fMRI), in which activation of the auditory association cortex of language is seen in the moment in which the patients present the hallucinations (for a detailed review, consult the papers of Kasai et al., 2002[14], and Font et al., 2003[15]).

The strategy of computer simulation is not based on simulating the complete syndrome that characterizes schizophrenia, but only on a symptom of this disease: auditory hallucinations.

Thus, some aspects of the perception system were simulated to determine if the pruning of the system connections (that feigned the corticorticals) could generate auditory hallucinations. This has been reproduced with fMRI in patients with schizophrenia, showing evidence of reduced frontotemporal functional connectivity, which was associated to auditory hallucinations but not to the presence of delusions[16].

The criterion to identify a «hallucination» in the computerized system was the production of perceptions in it in absence of any input phonetic signal.

The process involves work memory that uses expectations based on previous words and sentences to distinguish new verbal sounds or phonemas and transform them into words with meaning.

Many studies have demonstrated the impairment in working memory of schizophrenic patients[17,18]. Some authors have implied that this impairment involves interactions between frontal and medial temporal areas[19], which are known to be involved in working memory[20]. Due to this, the neuronal network will focus on the working memory component to examine the effects of the decrease in corticocortical connectivity.

Simulation of the neuronal network arose due to the observation that common language, when produced at normal speeds, has an important phonetic ambiguity due to confusion between phonetic information and underlying background sounds[21,22]. Thus, perception of a word inserted within narrative language not only depends of the input information corresponding to the word itself but also to the previously received words and intrinsic knowledge of how words are sequenced in major language units[23]. The use of linguistic expectation of the word learned to filter the auditory input of language reflects an important capacity in the working memory, which was incorporated into the neuronal network. Working memory is involved in the normal perception of language.

The cerebral systems are made up of a large number of interactive neuronal elements that have been usefully examined by computerized simulation[24]. Simulation of a neuronal network for the simulation of the narrative perception of language is explained in this dynamics. Although this simulation oversimplifies the large range of cortical processes involved, it has provided new knowledge on the normal neurodevelopment and the induction of psychosis.

These models have been used to try to explain the positive symptoms of schizophrenia as an abnormality in inner feedback to distinguish between external and self-generated stimuli[25] or in neurodevelopment[26], the latter being the one focused on in this study. This study aims to use the computerized model to reproduce, describe and simulate auditory hallucinations provoked by decrease in synaptic connectivity during development, which is a theory proposed for the development of schizophrenia. This will be done by following the model originally described by Elman for the neuronal unit[23,27] and the network published by Hoffman and McGlashan[26].

METHOD

A PC computer with Pentium III process at 533 mHz with Windows ME system and computer program MATLAB version 5.3 with Neural Networks Toolbox (http://www.mathworks.com/products/neuralnet/) was used to simulate the neuronal network.

The network consisted in 148 neuronal elements divided into a four layer system (fig. 1). This system was used to translate the «phonetic» input into words. To do so, it was assumed that the phonetic representation of each word corresponds to a single pattern of randomly generated activation.

To feed the network, words assigned by a binary code or «bits» of 25 combinations of zero and one numbers were used. Words in English were used since it is the language that the program manages and the grammatical rules are easier than if the Spanish language were used as the basis.

INPUT PATTERN

Coding of the sentences randomly was performed first to form this vocabulary. As each word has a coding of 25 bits, a matrix of 29 (words) × 25 (bits) was formed randomly and rounded to «0» and «1»: woman 11101011110011101111 0111, Jane 001011011 1101010101000000, etc.

The vocabulary created for the network consisted in 29 words, which included 15 nouns (woman, Jane, boy, girl, Bill, man, cop, Sam, omen, warning, story, dog, god, ball), 11 verbs (chase, kiss, love, fear, tell, run, kick, give, frightens, think, miss) and 4 adjectives (young, old, large, small).

Each one of the 40 neurons of the hidden layer received the sum of the input weights of the 25 input neurons and the 40 neurons of temporal storage that are equivalent to working memory.

Activation of each neuron of the hidden layer was calculated with a sigmoidal function that went from 0 to 1 and that acted on the sum of the inputs. The output layer consisted in 43 neurons, which received inputs exclusively from the hidden layer (fig. 1) and had the same sigmoidal activation function as the hidden layer neurons.

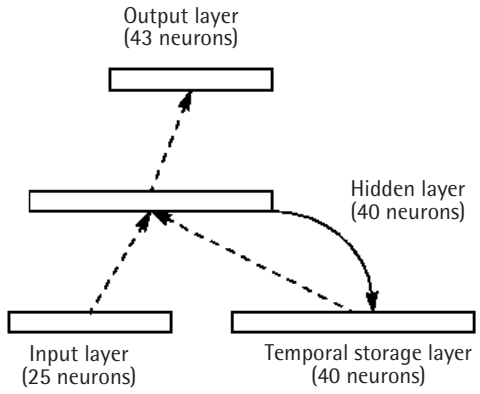

Figure 1 | *Outline of the neuronal network of 148 elements.*

Besides assigning a phonetic code, each word was assigned a pattern in the output layer, in which 3 to 6 neurons were activated. These neurons coded for the syntactic and semantic characteristics. For example, the word «man» was represented by the activation of the output neurons that individually codified for the grammatical characteristics of the word (noun, human, etc.) and a neuron specifically that also coded «man».

When the network produced an activation pattern of the output layer, an algorithm decided which word best corresponded to this specific pattern. What corresponds to this word best became the «detected word». When the activation pattern did not find a clear correspondence, the network did not detect any word.

Initially, a routine of forming sentences was programmed, first beginning with the coding of the sentences and creating a matrix randomly, assigning the correspondences for subjects, verbs and adjectives and their individual codings.

Once the coding for each word was defined, vectors were formed by type of word, that is, by subject, verb, etc. There were approximately 3,400 sentences after all the possible combinations were formed.

Each sentence has a structure: adjective + subject + verb + subject following the grammatical structure of the English language.

Once the 3,400 sentences were obtained, 300 final sentences were chosen randomly. These were then used to train the system, using 300 repetitions. These progressively minimized the error of the activation patterns produced by the output layer in response to the inputs whose phonetic information was partially degraded. During the training, the network acquired the skill to use linguistic expectations to be guided in the detection of words (stored as activation patterns resounding between the hidden layers and temporal storage, simulating the working memory).

Once the network was trained, it was re-examined with 300 sentences different from those previously used in the training, but in which the same vocabulary was used. During this new phase, the sentences identified that could not be used were counted (when one word was confused for another). To do so, two bits of the inputs different from those initially used were changed, which forced the system to recur more to working memory and the linguistic expectations to be able to correctly detect the words. Before the change in the 2 bits, 204 sentences of the 300, which were equivalent to 68 %, were correctly detected. Once the bits were modified, 62 % efficiency was found in the correct detection of the words, which indicates an acceptable level of functioning of the network. When the system identifies a word without having an input, this is considered a hallucination.

MANIPULATION OF THE NEURONAL CONNECTIONS (SYNAPSIS)

Two types of manipulation in the neuronal network structure were simulated: the first consisted in the elimination of the synapsis according to the absolute value of the weight they had and from less to greater weight, following the Darwinian model of natural selection in which the weakest interneuronal connections are eliminated, so that the synapses having the greatest weight will be left. These must be considered for the final determination of the pruning percentage. The second was the elimination of the neurons randomly.

RESULTS

The pruning effect in the neuronal connections is shown in figure 2. As the synapses were eliminated, the correct detection percentage increased from 68 % to 91 %, reaching the peak when there was an approximate elimination of 60%. When the elimination was continued with, detection capacity decreased, and words began to appear in the absence of input, which is considered as a hallucination. These occurred more frequently when pruning reached from 80 % to 95 %.

On the other hand, when the neurons were eliminated instead of the connections, the system worsened gradually in regards to detection of the words and no hallucinations occurred (fig. 3).

DISCUSSION

The cerebral systems were made up by a large number of interactive neuronal elements that had been usefully examined by computerized simulation. In this dynamics, the simulation of a neuronal network is explained for the simulation of narrative perception of language and working memory on programming the neuronal network for processing input signals degraded into identifiable words to then replicate the simulation model of auditory hallucinations and determine the effect of the synaptic pruning.

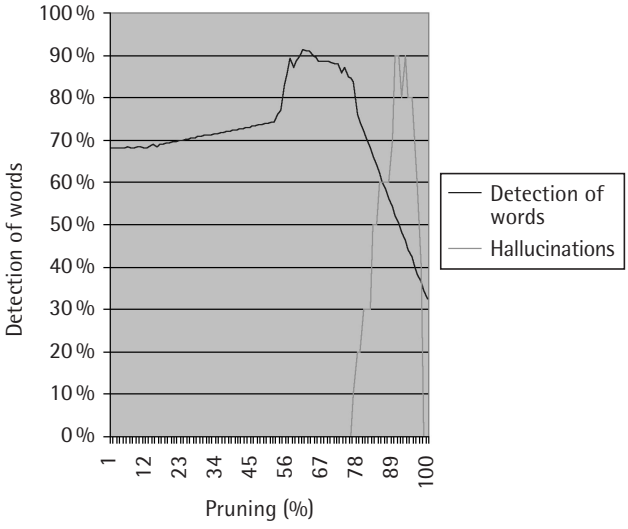

Figure 2 *Graphic representation of pruning phenomenon.*

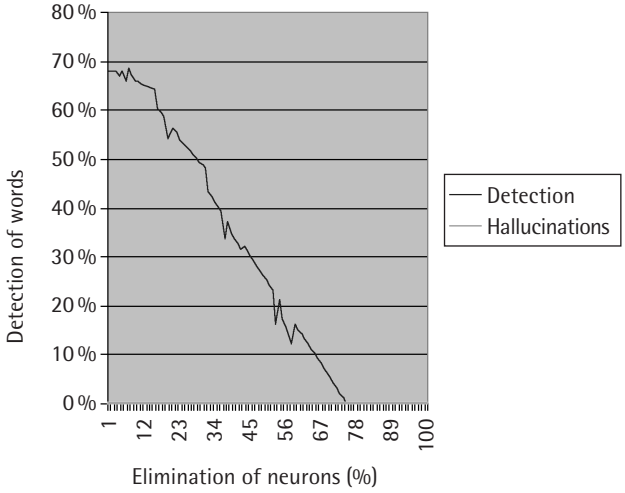

Figure 3 *Chart of elimination of the neuronal units.*

The findings of this study indicate that the initial detection of the degraded words in the system improved when up to 60 % of the synapses were eliminated. However, it was observed that elimination above 65 % conditioned a progressive dysfunction in the detection of words by the network. Following the natural selection Darwinian model in which the neurons compete for anatomic access with other neurons forming multiple synapses and eliminating the weakest interneuronal connections, it was decided to eliminate the synapses in this model according to the absolute value of the weight they had, progressively eliminating the synapses from less to greater weight. Considering that the weight is conditioned by the synapsis number, connections with a greater number of synapses represent the strongest interneuronal connections. Based on the distribution of the weights of the network that was not pruned, a 60 % connectivity reduction corresponds to a 29 % synaptic reduction, which is similar to that which occurs in the normal neurodevelopment in which a 30 % and 40 % reduction of the synapses in the frontal areas is observed[4], improving the language perception capacity[26,28,29]. On the other hand, it was observed that when more than 75 % of the synapses were eliminated, the model began to simulate hallucinations and these were clearer when 80 % of elimination was reached. This percentage of synapsis elimination, considering the weight of the non-eliminated neurons, corresponds approximately to a reduction greater than 40 % of the synapses, representing excessive pruning and that supports the hypothesis of an alteration in the neurodevelopment

associated to schizophrenia. These findings allow us to establish that it was possible to replicate the original model of Hoffman and McGlashan[26] with similar results.

Furthermore, it was also observed that when the neuronal units were eliminated instead of the connections, progressive worsening of perception was obtained, a finding reported in the original model[26]. This finding seems to support the hypothesis proposed that the physiopathology of schizophrenia (and possibly other psychotic disorders) is found the connection between the neurons and not in the neurons themselves.

One of the hypotheses proposed is that auditory hallucinations arise in the neurocircuit used for perceptual processing of language. Normal perception of language is a complex task given by the high level of acoustic ambiguity of the daily language produced at normal levels in noisy settings. The process involves the capacity of working memory that uses the linguistic expectations based on previous words and sentences to distinguish new verbal sounds or phonemas and transform them into words with meaning.

Based on the results of the neural network computerized simulation model of auditory hallucinations of a neuronal network, a group of schizophrenics with hallucinations and another without them were evaluated with a cognitive battery, finding alterations in the perception of language in working memory[30]. Furthermore, in studies that have evaluated perception, this hypothesis is supported, demonstrating that patients with auditory hallucinations have a predisposition to experience sounds without meaning as language lacking meaning and to misinterpret the language with less phonetic clearness[31,32]. On the other hand, activation of the temporal region in patients with auditory hallucinations evaluated with fMRI has been demonstrated. This suggests that the hallucinations compete with external language[33]. Activation of the areas of left temporoparietal association has also been established just in the moment when the hallucinations occur[34], a finding corroborated in a single photon emission computed tomography study[35]. Because the temporal and parietal dominant areas participate in decoding language, the previous studies support the fact that auditory hallucinations come from the neurocircuits responsible for language process[36].

The computerized simulation model not only provides a model for the formation of symptoms but also of an understanding of the adaptive utility of pruning. It would seem that it serves in learning, increasing cognitive capacity, sharpness, efficiency and rate of learning at the expense of loss of flexibility. Furthermore, it is a natural and necessary neurobiological process at the service of social, linguistic and intellectual functioning of man. This is how the optimal pruning could be related with advantages in adaptation and competiveness and could have a natural selection for survival in direction towards a maximum pruning with the risk of exceeding the threshold for psychosis.

With this model, different explanations for the pathophysiological of schizophrenia have been proposed. The disease onset occurs when a critically low synaptic connectivity is reached. Schizophrenia beginning in the early age arises when a synaptic network is exposed to an abnormally aggressive pruning process. On the other hand, when the disease appears after 30 years, it is due more to the result of a normal pruning in a person whose synaptic network is already close to the borderline threshold[28].

The computerized model identifies decreased synaptic density in the prefrontal areas and in other areas of the association cortex as the final common pathway of the symptoms and the course of schizophrenia and, perhaps, of other psychotic disorders (as affective psychoses or psychosis secondary to substances). In these, without presenting such serious symptoms as in schizophrenia, those presenting them could have a borderline neuronal network for psychosis but without exceeding the threshold for the development of a chronic psychotic disorder.

Since pruning is a constant variable, this model stresses the pathophysiology of neurodevelopment. Variability in baseline synaptic density is determined by genetics, perinatal stress and other processes. While the role of deficits in neurodevelopment and perinatal factors that affect neurodevelopment (viral infections, environmental stress, hypoxia, etc.) may be substantial, they are not sufficient to cause the disease. Thus, a second factor that may be normal or accelerated synaptic pruning is necessary.

As previously mentioned, these types of models do not aim to explain all the disease, however, it brings us increasingly closer to understanding one of the most devastating diseases affecting the human being to a greater degree.

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