Pathological effects of cortical architecture on working memory in schizophrenia

C.D. Gore\textsuperscript{a,b}, P.J. Gray\textsuperscript{a}, M. Bányai\textsuperscript{a,c}, V. Diwadkar\textsuperscript{d}, P. Érdi\textsuperscript{a,c}

\textsuperscript{a}Center for Complex Systems Studies, Kalamazoo College, Kalamazoo, Michigan, USA
\textsuperscript{b}Dept. Biophysics, KFKI Research Institute for Particle and Nuclear Physics of the Hungarian Academy of Sciences, Budapest, Hungary
\textsuperscript{c}Dept. Behavioral Neuroscience and Psychiatry, Wayne State Univ. Medical School, Detroit

Abstract

A reduction of neural connectivity levels in the prefrontal cortex has been shown to be a common characteristic associated with schizophrenia. Those with schizophrenia have also been shown to exhibit abnormal prefrontal dopamine modulation, which is thought to cause cortical pruning and greatly affect working memory performance. Working memory enables the storage of transient information for a relatively short period of time, another deficit common with schizophrenia. Two types of models are studied. First, the performance effects of cortical pruning were simulated with a set of scale-free networks of neurons and compared with results from a clinical test (Sternberg test) using a working memory task. The network showed that modulating levels of cortical pruning displays a gain or loss in accuracy and speed of memory recollection. This decline in memory performance can be attributed to the emergence of pathological memory attractor basins, which were illustrated by the model. Second, the synaptic theory of working memory is studied. Memory duration in terms of the synaptic facilitation and depression constants, and in terms of reduced connectivity was simulated. This paper demonstrates that a reduction of prefrontal cortical hubs can account for certain pathological working memory effects in schizophrenia.

1. Introduction

Working memory (WM) is an important cognitive function that refers to the maintenance and online manipulation of information for a short period of time. The prefrontal cortex has been shown [9] to play an important role in WM, although not all of the specific workings are entirely clear. Magnetic resonance imaging (MRI) tests suggest that, physiologically, a healthy person’s PFC should exhibit hubs of neurons, i.e. loosely speaking there are neurons with much more connections, than the average. Persons with schizophrenia are more likely to have hubs in areas outside the PFC instead [4]. It has also been seen that dopamine is a critical component for sustaining WM[9], and abnormalities in dopamine levels in the PFC are commonly associated with schizophrenia and may account for the development of delusional memories[10, 3, 6, 5], a common symptom of schizophrenia.

Pathological attractors may implement the dynamic generation of positive symptoms in schizophrenia as these symptoms, including delusions and hallucinations can be activated in the absence of external cues. Related to the modifiability of the attractor-basin portrait, a model based on the NMDA receptor delayed maturation has also been suggested as a possible mechanism of the pathogenesis of schizophrenic psychotic symptoms [7].

Dynamical systems hypotheses are based on the assumption that pathological symptoms are related to changes in the geometry of the attractor basin portrait [13, 8]. A network model of excitatory and inhibitory neurons built by leaky integrate-and-fire models was used to design several simulation experiments to study the effects of changes in synaptic conductances on overall network performance. Reduction in synaptic conductances connected to glutamatergic NMDA receptors implied flatter attractor basins, and consequently less stable memory storage. Combined reduction of NMDA and GABA receptors imply such changes in the attractor structure, that may implement such positive symptoms, as hallucinations and delusion.

Functional magnetic resonance imaging (fMRI) studies have demonstrated the PFC’s role in WM tasks. During clinical WM tasks, a stimulus is briefly presented to a subject often to be remembered during a delay period that takes place between the presentation of a stimulus and the execution of a task. An example of such a task is the Sternberg delay [20], where a subject is shown a string of capital, consonant letters (e.g., BGZXF) followed by a delay at which time they are prompted with a letter and a position (i.e., Z=3) and asked whether or not that particular letter was in the given position in the string. Sternberg found that in doing this test, the response time for patients increases almost linearly as the number of characters to remember increases. In a neuroimaging study using the Sternberg test [2], it was shown that activation in the dorsolateral PFC increases and also that, as the set size increases, the patients’ accuracy decreases and the response time increases almost linearly. The results of the study are reproduced in Figure 1.

Since cortical networks might have scale-free network features [15], we compared the performance of different scale-free networks in the to solve the Sternberg task. The question was whether a network architecture with smaller number of hubs
show a reduced performance. The simulation results answered the question with yes.

The "synaptic theory" of working memory [14] suggested that the duration and stability of the working memory depends on the balance of synaptic facilitation and synaptic depression. Calcium-dependent mechanisms might be responsible for changing the ratio between these two sub-processes. While the details of these mechanisms are not known, the memory duration in the two-dimensional parameter space of the rate constants were simulated. The effect of the systematic cortical pruning was also studied. Memory duration was found to fall first rapidly, then slowly by increasing connectivity.

!!! Some preliminary explanation is missing !!!!

2. Comparative studies on the memory performance of different scale-free networks

2.1. Generation and test of networks

At traditional Hopfield neural network connects neurons in an all-to-all fashion[11]. Of course biologically, this is not a very realistic representation. Since biological neural networks have been shown to develop complex architectures that share common properties with scale-free (SF) networks [15]. SF networks are evolving networks, so their architectures are built over many iterations. The vertices in the resulting networks have degrees $k$ that are distributed according to a power law $P(k) \propto k^{-\gamma}$, where $P(k)$ is a function describing a node's likelihood of receiving a new connection with each iteration. This results in a hierarchical architecture reminiscent of real cortical architectures, with most of the neurons represented as sparse nodes, having very few connections, and a small portion of the nodes acting as hubs, with many connections. This is a more desirable template for network architecture for investigating the role of hubs in maintaining stable memory states.

2.1.1. Implementation of the Sternberg task for scale-free neural network

The model employs the Barabási-Albert (BA) method [1] for building the network structure. A BA network has $N$ nodes and $m(N - n_0)$ edges. Here, $n_0$ is the initial number of nodes that seed the network with a fully connected graph, and $n$ (where $n \leq n_0$) is the number of connections added with each iteration of the algorithm. With the addition of each new node, previous nodes in the network probability of receiving a new connection described by the linear preferential attachment algorithm:

$$p_i = \frac{k_i}{\sum_j k_j}.$$  (1)

A set of networks were generated by choosing different values for $n_0$ and $n$. For the comparative studies presented here four networks were chosen. The generated networks are characterized by the degree distributions shown in Figure 2.

Now we turn to explain how to test the generated networks. Patterns are created for the Sternberg delay by generating sets of 3, 5, and 8 random consonants. Consonants are represented by their numerical equivalents in binary form, using five binary digits per letter. These patterns are made larger by a multiplier, 15 in the case of the tests, as illustrated in Figure 3. Any space remaining to make 600 digits is filled with zeros to the left of each pattern.

The binary units are normalized to a range of -1 to 1 each, and a weight matrix is generated following the Hebbian learning rule

$$\omega_{ij} = \sum_{k=1}^{p} x_i^k x_j^k,$$  (2)

assigning a synaptic strength $w_{ij}$ to each network connection. Each weight matrix is mapped across a randomly generated BA graph, removing connections without corresponding edges.
Degree (k) pathology of “pathological attractors”, and unlearned
ies have shown that cortical pruning may lead to the for-
cessive pruning of cortical connections. Simple network stud-
would be 000000 01101 00000 00000 00000.
For example, in figure 3, the cue for the second character M
original pattern and running until convergence or divergence.
run for each set of parameters and set size and the results av-
eraged. The behavior of the model’s results, shown in Figure
4, show the relationship between nodal degree and memory
performance. Networks with stronger hubs remember patterns
more accurately and more quickly.
Table 1 shows a comparison of various degree levels, be-
tweenness, $n$, $n_0$, and average number of pathological attrac-
tor basins. It is clear that pathological attractors develop when
there is less nodal clustering.

3. Synaptic theory of working memory: some further stud-
ies
3.1. The model framework
The synaptic theory of working memory was suggested by
[14]. A simple model for the the prefrontal cortex was speci-
ified, exploiting the general belief, that in this brain region the
excitatory synapses are facilitatory. Working memory is gener-
ated and maintained by short-term synaptic facilitation.
A reduced short term plasticity model uses two variables, $x$
is the available resource (releasable transmitter molecules) and
the $u$ is the utilization variable (residual calcium level). The in-
crease of $u$ is called the facilitation, and the decrease of $x$ is the
depression. The terminology is not fortunate, since the product
$ux$ characterizes the synaptic change. The process is controlled
by two time constants: $\tau_f$ and $\tau_d$ denotes the facilitatory and
depressive time constants, respectively. The model is defined
by the equations 5.

$$\frac{dx}{dt} = \frac{1 - x}{\tau_D} - u \delta left(t - t_{sp\text{right}})$$
$$\frac{du}{dt} = \frac{U - u}{\tau_F} + U \delta left(1 - \text{right}) \delta left(t - t_{sp\text{right}})$$

In [14] the time constants were fixed as $\tau D = 0.2s$ and $\tau F =
1.5s$ to express facilitation.
Our research project started, as [14] stopped: ”...The model
provides a possible target for a pharmacological interference
with WM. In particular, manipulations that modify the facilita-
tion/depression balance in the memory-related cortical areas...
are predicted to have a strong effect on the stability and duration
of memory.”
3.2. What processes might regulate the time constants?

Calcium binding proteins (say neuronal calcium sensor NCS-1) modify short-term plasticity (at least hippocampal cell cultures) by switching pair-pulsed depression to facilitation [21]. Since facilitation seems to be “normal”, we might expect that NCS-1 concentration should be large for normal patients, and low for schizophrenic. However, NCS-1 is up-regulated in PFC of schizophrenic patients [18] and it looks paradoxical: facilitatory synapses should be normal and not “schizophrenic”. The molecular machinery might be much more complicated: (i) NCS-1 might be double localized pre- and postsynaptically [12], (ii) NCS-1 is a part of a network of proteins.

Since we are far from being able to give a realistic detailed mechanism for changing the balance between facilitation and depression, we studied the dynamic properties of the system in the two-dimensional parameter space of the time constants. To evaluate the performance of the memory system we had to define the duration of the memory. The hypothesis was that the shift in the balance between facilitation and depression might modify the duration of the memory. Phenomenologically two types of pathology, “too short” and “two long” could be defined. The questions to be answered is how the duration of memory depends on the two time constants, and the reduced connectivity, respectively.

3.3. Definition of duration of working memory

Time between the end of the write-in signal (the population-specific increase in the background input that loads an item to the memory) and the last time point when we can retrieve the object from the memory.

Retrieval: a readout signal (a nonspecific increase in the background input), the used population will produce a population spike (PS) and the others do not.

This PS codes for the object loaded in the memory previously and refreshes the memory as well. The probability of observing a PS is mostly dependent on the actual level of synaptic efficacy. We can define a threshold value in efficacy that divides the two behaviors of the network (PS or not). So we can define the duration as the time between the endpoint of the write-in signal and the time-point when the efficacy falls under the threshold value.

3.4. Results

First, the two-dimensional parameter space was explored, as Figure 5 shows. The result is quite intuitive, if the facilitation relaxes slower and the depression relaxes faster, the memory duration will increase. Probably one can define a regime that can be considered normal, and there are two regimes for too short and too long memory fading time.

Second, the connectivity was changed by setting the overall connection probability from 0 to 0.8. Somewhat counterintuitively, the duration was reduced by increasing the connectivity, as one can see in Figure 6. However, if we take a look at the model setting, the cause for this behaviour is obvious. We apply an external input on all the cells that is modelled by a Gaussian noise with a large
mean and small deviation. The mean is actually above the firing threshold of the cells, so if there were no other dynamics, they would fire permanently with a frequency defined by the refractory period. The principal effect of the cells on each other is the inhibition, allowing them to follow different firing patterns.

4. Discussion

Computational studies of the reduced cognitive abilities of schizophrenic patients were presented previously [17, 22, 16]. In this paper further examples were given to uncover the details of the structure-function relationship behind schizophrenia. A loss of neural hubs in the PFC was observed in schizophrenic patients[4]. The Sternberg delay [20] proved to be a good working memory exercise, utilizing the PFC [2]. Modulating network generation parameters in order to vary the average nodal degree proceed the predicted pathological attractor basins. Along with warping the energy function, these pathological attractors proved to have a strong impact on the resulting networks’ accuracy and time to recall a pattern.

Acknowledgments

PE thanks to the Henry Luce Foundation for general support.

References


