Cortical Pruning and the Development of Schizophrenia: A Computer Model

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Abstract

Schizophrenic patients tend to demonstrate reduced cerebral metabolism in frontal areas. Studies of human brain development reveal that synapses in the cerebral cortex are progressively reduced throughout childhood and adolescence, with parallel reductions in cerebral metabolism. This relationship is not surprising, since synaptic density is a primary factor determining regional metabolic requirements. The elimination of synapses in prefrontal cortex continues for a particularly long period of time, extending well into adolescence. Thus, reduced frontal metabolism in schizophrenic patients could be due to a developmental process—namely, elimination of synapses—gone too far. Animal studies indicate that developmentally induced reductions in synaptic density are due to the pruning of axonal collaterals rather than the death of neurons, which raises a critical question: Does excessive axonal pruning have specific pathological effects on cortical information processing? To answer this question, computer simulations of neural information processing systems were subjected to axonal pruning which reduced synaptic density. If pruning was conducted overzealously, cognitive pathology was induced that could, in humans, lead to the conscious experience of hallucinations, delusions, and Schneiderian symptoms.

Relating the signs and symptoms of schizophrenia to underlying brain processes remains a major research challenge. These efforts must link two distinct categories of events—the former belonging to the realm of mental phenomena, and the latter being physical phenomena. Computer simulations of neural network interactions are now offering clues about how biologically characterized events can accomplish cognitive tasks. Variants of these models may reveal how disordered neural processes can yield particular kinds of disordered cognition. This report critically examines a number of biological studies of schizophrenic patients in the context of recently emerging knowledge of human brain development. A particular neuroanatomical disturbance is hypothesized on the basis of this review. A computer simulation of this neuroanatomical disturbance is then presented to characterize the resultant psychopathology.

Reduced Cerebral Metabolism in Schizophrenia

Studies of schizophrenic subjects using positron emission tomography and cerebral blood flow measurements often suggest diminished metabolism in frontal areas (Ingvar and Franzen 1974; Buchsbaum et al. 1982, 1984; Ariel et al. 1983; Farkas et al. 1984; DeLisi et al. 1985; Wolkin et al. 1985, 1988; Chabrol et al. 1986; Weinberger et al. 1986). Other reports did not confirm so-called "hypofrontality" in these patients (Mathew et al. 1982; Gur et al. 1985, 1987; Jernigan et al. 1985; Kling et al. 1986). As pointed out by Buchsbaum and Haier (1987), three of these negative studies (Mathew et al. 1982; Jernigan et al. 1985; Kling et al. 1986) still demonstrated trends in the direction of hypofrontality even though statisti-

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cal significance was not attained. Two of these negative studies (Mathew et al. 1982; Gur et al. 1987) demonstrated reduced cerebral metabolism *overall* in schizophrenic patients in spite of the absence of statistically significant abnormalities attributable to frontal areas; two studies that did find evidence of hypofrontality in schizophrenics also showed an overall diminution in cerebral metabolism (Ariel et al. 1983; Wolkin et al. 1988). These various reports differ in subject selection, technique, and experimental conditions, and therefore are not strictly comparable. Nonetheless, the overall pattern of the results has been fairly consistent, and suggests that reduced cerebral metabolism can be found among many schizophrenic patients, particularly—but perhaps not exclusively—in frontal areas.

These metabolic findings raise three questions:

- *What causal factors contribute to hypofrontality in schizophrenia?* X-ray computed tomography has indicated that there is a subgroup of schizophrenic patients who demonstrate ventricular dilatation (for review, see Waddington [1985]), suggesting that hypofrontality is due to frank tissue loss. Although one study demonstrated a statistically significant negative correlation between ventricular dilatation and frontal metabolism (Jernigan et al. 1985), four other studies did not (DeLisi et al. 1985; Brodie et al. 1986; Kling et al. 1986; Wolkin et al. 1988). Moreover, postmortem neuropathological studies of cortical tissue from schizophrenic patients do not reveal a frank neurodegenerative process specific to frontal areas (Stevens 1982; Benes et al. 1986). Thus, large-scale tissue loss seems not to be the primary contributing factor to hypofrontality.
- *Is hypofrontality a cause or an effect of schizophrenia?* Wolkin et al. (1985) present data indicating that hypofrontality persists after treatment, suggesting that the phenomenon is relatively stable. Nonetheless, whether hypofrontality is a vulnerability factor predating the onset of illness or somehow evolves during the course of the disorder is completely unknown.
- *Are neurometabolic findings related to the characteristic symptoms of schizophrenia?* Frontal lobe disturbances secondary to neurological lesions frequently bring about attentional impairments, affective flattening, and reduced motivation (Fuster 1980). These manifestations have been identified as "negative" symptoms of schizophrenia; two studies have indicated that these symptoms positively correlate with ventricular dilatation (Johnstone et al. 1976; Andreasen et al. 1982). It is not at all clear, however, what causal factors contribute to the classical "positive" symptoms (hallucinations, delusions, and thought disorder) of schizophrenia. The significance of metabolic findings in schizophrenia would be enhanced if they shed light on this more enigmatic side of the disorder.

Recent research findings in developmental neurobiology offer an approach to answering these questions.

Axonal Pruning During Postnatal Cortical Development

The human cerebral cortex can be thought of as two folded-up multilayered sheets of neurons, each with an area of approximately 1,000 cm^2 (Crick and Asanuma 1986). In comparison, this figure for the macaque monkey is approximately 100 cm^2. A major portion of this upward shift in cortical area through evolution is referable to prefrontal areas. Prefrontal cortex does not receive any direct sensory input, and therefore is dependent on projections from other cortical areas for input information.

A post-mortem study by Huttenlocher (1979) has demonstrated that large shifts occur in the synaptic density of layer III of the prefrontal cortex throughout childhood and adolescence in humans. His data indicate that synaptic density in this cortical area increases from birth until ages 5–7 and then gradually declines—by 30 to 40 percent—with stabilization to adult levels occurring at around 16 years of age. A number of neuroanatomical studies in animals have shown that cortical development involves progressive reductions of corticocortical axonal projections (Innocenti 1981; O'Leary et al. 1981; Ivy and Killackey 1982). These reductions are not mediated by cell death, but by elimination of axonal collaterals; this process will be referred to as *axonal pruning*. It is likely, in light of these findings, that axonal pruning is a major cause of the progressive reduction of prefrontal synapses between midchildhood and adulthood originally noted by Huttenlocher; the effects of axonal pruning on synaptic density are analogous to reducing the number of leaves on a tree by eliminating some of its branches.

The developmental profile of synaptic density for layer III of human prefrontal cortex is probably generalizable to other cortical layers and other areas of cortex. A later study of synaptic density in human visual cortex revealed the same longitudi-

nal pattern of an early peak followed by a progressive decline (Huttenlocher et al. 1982). However, the process in visual cortex was somewhat accelerated in comparison to that of the prefrontal cortex, with maximum synaptic density for the former occurring at around 1 year, and stabilization to lower adult levels at approximately ages 11–12. A recent developmental study of rhesus monkeys by Rakic et al. (1986) also found that there is rapid synaptogenesis to peak levels followed by progressive synaptic loss. This study is noteworthy insofar as many different cortical regions and all cortical layers demonstrated this developmental pattern. It is likely, therefore, that developmentally induced shifts in synaptic density in humans involve all cortical layers and regions.

The Huttenlocher studies of synaptic density profiles during childhood development required electron microscopic examination of cortical tissue. A more global, metabolic dimension of brain development has also been characterized. Using positron emission tomography in children, Chugani et al. (1986) have found that cerebral metabolism peaks between 3 and 7 years of age and then drops by approximately 50 percent to adult levels. Unfortunately, regional metabolic changes have been less well characterized during older childhood and adolescence. However, in early childhood, a developmental lag was noted in frontal areas compared to visual cortical areas in achieving peak regional metabolic levels (Chugani and Phelps 1986). Of great interest is that a similar developmental lag for upward shifts in synaptic density in frontal versus visual cortex was found at a microscopic level during early childhood (Huttenlocher 1979; Huttenlocher et al. 1982); these parallel shifts in regional cerebral metabolism and synaptic density over time suggest a causal linkage (Phelps and Chugani 1986). This hypothesis is supported by physiological data indicating that nerve endings have significantly greater metabolic requirements in comparison with other microanatomic components of neurons such as cell bodies (Mata et al. 1980). It is likely, therefore, that reductions in synaptic density relative to total neural tissue volume would diminish regional metabolism.

If synaptic density and regional metabolism are coupled phenomena, schizophrenic hypofrontality could reflect a pathological reduction in synaptic density in prefrontal areas. This could occur via a pathological extension of developmentally induced axonal pruning during adolescence; synaptic reductions during adolescence tend to involve prefrontal cortex preferentially; a failure to turn off this developmental process would therefore be expressed as hypofrontality. This developmental model of schizophrenia answers the first two questions raised earlier. First, the model explains how hypofrontality could occur in the absence of findings indicative of a gross neurodegenerative process—developmentally induced reductions in synaptic density seem to be due to axonal pruning rather than large-scale neuronal death and gliosis. Second, if the model is correct, hypofrontality reflects a longstanding developmental process run amok. Moreover, the fact that the onset of schizophrenia generally occurs in late adolescence or early adulthood is accounted for—this would be the time when the cumulative effects of axonal overpruning would first be fully felt.

Computer Simulations of Neural Information Processing

This developmental model provides answers to the first two questions posed above, but not the third—namely, whether reductions in cerebral metabolism can be linked to the classical "positive" symptoms of schizophrenia. This aspect of the model, however, can be appreciated via a branch of computer science known as artificial intelligence (AI). AI, in popular culture, is still largely equated with robots and machines that talk. However, a quiet revolution is occurring among researchers who explore human thought by attempting to devise computational devices that are capable of cognitive tasks.

Ten years ago most researchers in AI were working with "classically designed" computers. These computers, ranging from desktop PCs to large mainframe devices, all work essentially the same way. Steps in the "program"—the internalized instructions for completing some task—are executed *sequentially*, one step at a time. The power of the computer, to a large extent, is determined by how fast each step is performed.

Such devices readily "crunch" through extremely complex mathematical computations. However, sequential computers do not easily lend themselves to a variety of cognitive tasks that seem quite simple and natural to us. Underlying many of the standard computer's cognitive difficulties is how they access memories. In general, these computers recall a memory via a name or specific instructions indicating where the desired memory is "located" in storage. For instance, suppose a standard computer stores memories of historical figures. If we give the computer the name

"Nathan Hale," the memory corresponding to the person, Nathan Hale, would be readily retrieved. Suppose, however, that we asked the computer, "Who said, 'I only regret that I have but one life to give to my country'"? The standard computer would have to peek sequentially into each stored memory. When this particular utterance of Nathan Hale was found, the search would finally terminate, and the computer would produce the answer.

This laborious method of memory recall does not seem well suited for human cognition when one out of a large number of memories is to be retrieved on the basis of a portion of the memory. The mere sound of a voice or a silhouette of a face can immediately recall the identity of a whole person among all the persons that one has known; a whiff of clover recalls a childhood memory which included the smell, and which somehow is plucked from the set of all childhood memories. Systems that are able to use a part of a memory to gain immediate access to the whole memory without sequential search are called *content-addressable* memory systems. This type of memory retrieval seems critical for cognitive operations ranging from simple facial recognition to complex problem solving whose solution requires matching new problems to old ones whose solutions are known.

Given that sequential computers have built-in difficulties in retrieving information via content rather than name, AI researchers have developed other computer architectures that embody content-addressable memory systems in a more natural and direct fashion. These computers tend to consist of a large number of simple, interactive computing units that operate *in parallel* (Hopfield 1982; Hopfield 1984*a*, 1984*b*; Ackley et al. 1985; Hopfield and Tank 1986; Rumelhart et al. 1986). An increasing body of research suggests that the functional architecture of mammalian cerebral cortex is best characterized as a large number of neuronal units communicating together and acting in parallel (Ballard 1986; Hopfield and Tank 1986; Sejnowski 1986; Skarda and Freeman 1987; Goldman-Rakic 1988). This is not surprising given that parallel architectures, on the basis of what is currently known, seem optimal for realizing content-addressable memory capabilities required for so many different cognitive tasks.

Parallel-designed neural network models of content-addressable memory described by Hopfield (Hopfield 1982, 1984*a*, 1984*b*; Hopfield et al. 1983; Hopfield and Tank 1986) have recently been shown to be useful in exploring associative disturbances in schizophrenia (Crick and Mitchison 1983; Hoffman 1987*a*). The number of neurons in Hopfield simulations have ranged between 20 and 10,000; these simulations have assumed that each neuron receives synaptic input from all other neurons. Postsynaptic effects can be either excitatory or inhibitory. As the number of neurons increases, the complexity of connections becomes enormous. Since all neurons are constantly interacting with each other, the classical notions of feedback and feed forward loops and controls are no longer applicable, and new concepts are needed to predict the behavior of these systems.

Hopfield used small particle physics to understand and predict the behavior of these neural systems, and he demonstrated that they are analogous to physical systems of interacting molecules where molecules are bumping into each other and modifying each other's behavior. The behavior of a Hopfield network can be intuitively thought of as a physical system that tends to orient itself in certain stable "crystalline" structures. In the neural network, these structures correspond to specific, reproducible patterns of activation for the different neurons of the system. Insofar as these activity patterns are reproducible, they can be thought of as memories of the system. In terms of the "I have only one life to give to my country" problem, this bit of information would act as a "seed" that would immediately provoke the crystalline structure that encodes the stored information pertaining to Nathan Hale—without requiring any sequential search of alternative memories.

To prepare the reader for the computer simulation study that will be discussed in the next section, a simple example of a Hopfield neuronal network will now be presented. Let us assume that the system is composed of 16 neurons arranged in a 4 × 4 square. Each neuron periodically adjusts its internal state on the basis of current synaptic input from the other 15 neurons in the system. At any particular time, the state of each of the neurons is considered to be either "activated" or "suppressed" and is represented as either 1 or -1; the state of each neuron will be referred to as μ_{ij}.

The synaptic strength, $T_{xy \rightarrow ij}$, linking neuron (x,y) to neuron (i,j) is a scalar weight which determines the effect of the former on the latter. Synaptic strengths linking neurons can be either positive (i.e., excitatory) or negative (i.e., inhibitory). The absolute value of synaptic strengths specifies the extent that one neuron affects

another. The collective contribution of synaptic inputs to neuron (i,j)—represented below as E_{ij}—from the other neurons in the system is as follows:

$$(1)\ E_{ij} = \Sigma T_{xy \rightarrow ij} \mu_{xy} \quad x,y = 1 \text{ to } 4$$

The neural sheet moves in *cycles* where the state of each neuron is reassessed and adjusted according to its synaptic inputs specified by equation (1).[1] If the synaptic input is >0, then the neuron is "activated" for the next cycle; that is, the state is reset to 1; if the synaptic input is ≤0, the neuron is deactivated; that is, its state is reset to -1.

An individual memory in a Hopfield system corresponds to an activation pattern specifying the state of each neuron in the system. Each memory can be thought of as a unique bundle of features where each neuron specifies the presence/absence of a feature. Memory storage occurs by examining each pair of neurons in the system. If the state of two neurons is the same for the memory (either 1/1 or -1/-1), then the synaptic strength linking these two neurons is made more positive. If the states of the neurons are different (either 1/-1 or -1/1), then the synaptic strength linking these two neurons is adjusted in the negative direction. This procedure, carried out for each pair of neurons in the system and for every memory, can be represented by the following equation:

$$(2)\ T_{xy \rightarrow ij} = \sum_{m} \mu^{m}_{ij} \mu^{m}_{xy}$$

where $T_{xy \rightarrow ij}$ is the synaptic weight linking neuron (x,y) to (i,j), and μ_{ij} is the state of neuron (i,j) for memory m. For example, suppose a 4 × 4 neuronal network stores the following three memories:

Memory #1	Memory #2	Memory #3
-1 1 1 -1	-1 1 -1 1	-1 -1 1 1
1 -1 -1 -1	-1 -1 -1 -1	-1 -1 1 1
1 -1 -1 -1	-1 1 1 1	1 1 1 -1
-1 -1 1 1	-1 1 -1 -1	-1 -1 -1 1

To compute the final $T_{xy \rightarrow ij}$, equation 2 states that for each pair of neurons, the state of the first neuron of the pair is multiplied by the state of the second neuron for each memory, and then summed across all three memories. Thus:

	Memory #1	Memory #2	Memory #3
$T_{11 \rightarrow 11}$ =	1x 1	+ 1x 1	+ 1x 1 = 3
$T_{21 \rightarrow 11}$ =	-1x 1	+ -1x 1	+ -1x-1 = 1
$T_{31 \rightarrow 11}$ =	-1x 1	+ -1x-1	+ -1x-1 = 1
$T_{41 \rightarrow 11}$ =	-1x-1	+ -1x 1	+ -1x 1 = -1
$T_{12 \rightarrow 11}$ =	1x-1	+ -1x-1	+ -1x-1 = 1
$T_{13 \rightarrow 11}$ =	-1x-1	+ -1x-1	+ -1x-1 = 3

In this fashion, synaptic strengths linking all 16 × 16 = 156 neuronal pairs can be determined; in this simulation each neuron loops back and has a synaptic effect on itself. Synaptic strengths according to equation 2 are symmetrical, that is, $T_{xy \rightarrow ij} = T_{ij \rightarrow xy}$. As a result, the complement of each memory is stored as well as the memory itself. The complement of a memory is its mirror image, i.e., wherever μ_{ij} is 1, it becomes -1 and vice versa. Hopfield systems without this functional symmetry have interesting properties (Hopfield 1984*a*) but were not explored in this study.

To demonstrate associative memory capabilities, the network is provided with a portion of one of the memories. For instance, let us set the four uppermost neurons of the system to match that of Memory #1 and leave the state of the other neurons indeterminant by setting them to 0. This initial state of the system is as follows:

Starting State

-1	1	-1	1
0	0	0	0
0	0	0	0
0	0	0	0

The next step is to determine the synaptic input to each neuron on the basis of this startup information. Looking at neuron (1,1) first, the state of each neuron, μ_{xy}, is multiplied with $T_{xy \rightarrow 11}$, and added together; this is the computation corresponding to equation 1:

$$E_{11} = T_{11 \rightarrow 11} \times \mu_{11} + T_{12 \rightarrow 11} \times \mu_{12} + T_{13 \rightarrow 11} \times \mu_{13} + T_{14 \rightarrow 11} \times \mu_{14} + T_{21 \rightarrow 11} \times \mu_{21} + T_{22 \rightarrow 11} \times \mu_{22} + \text{etc.} = 3x\text{-}1 + \text{-}1x1 + 1x1 + \text{-}1x\text{-}1 = -2$$

(*Note:* all synaptic contributions from other than first row are 0)

When the synaptic input is computed in this fashion for each neuron, the following matrix is derived:

$$\begin{matrix} E_{11} & E_{12} & E_{13} & E_{14} \\ E_{21} & E_{22} & E_{23} & E_{24} \\ E_{31} & E_{32} & E_{33} & E_{34} \\ E_{41} & E_{42} & E_{43} & E_{44} \end{matrix} = \begin{matrix} -2 & 6 & 6 & -6 \\ 6 & -2 & -6 & -6 \\ 2 & -6 & -6 & -2 \\ -2 & -2 & 6 & 2 \end{matrix}$$

If the synaptic input, E_{ij}, is >0 on this cycle, then the neuron is turned "on"; otherwise it is turned "off." Consequently, the state of the system is converted to

-1	1	1	-1
1	-1	-1	-1
1	-1	-1	-1
-1	-1	1	1

This is the neuronal activation pattern corresponding to Memory #1. Thus, the original input state that began with a portion of the memory was therefore able to naturally re-create the whole memory. Sim-

[1] This differs from the original Hopfield model where each neuron adjusts its state asynchronously; our pilot data indicated that networks whose states readjust cyclically behave similarly to networks whose states readjust asynchronously.

ilarly, a starting state that includes a portion of Memory #2, using the same set of synaptic strengths, will yield the following synaptic inputs and readjustment state:

Starting State	Synaptic Inputs for Next Cycle	Readjustment State
-1 1 -1 1	-6 2 -6 6	-1 1 -1 1
0 0 0 0	-6 -6 -2 -2	-1 -1 -1 -1
0 0 0 0	-2 6 6 2	-1 1 1 1
0 0 0 0	-6 2 -6 -2	-1 1 -1 -1

Even though the starting state in the second case differed from the first case for only two neurons, the system flowed to an entirely different—and correct—configuration matching Memory #2.

Metabolic studies of schizophrenia, when considered in the context of neurodevelopmental studies in normal children and adolescents, suggest excessive synaptic density reductions in prefrontal areas. Cortico-cortical connections in prefrontal cortex involve neurons in layers III, IV, and VI (Szentagothai 1978; Goldman-Rakic 1988). Developmentally induced synaptic density reductions in animals and probably also in humans involve all six cortical areas (Rakic et al. 1986), including the three layers just mentioned. If this is the case, pathological reductions in prefrontal synaptic density would reflect reductions in cortico-cortical connectivity as well. Our interest in interneuron connectivity was also spurred by the biological implausibility of Hopfield's original neuronal network simulations whereby each neuron is assumed to be synaptically connected to every other. We hypothesized that Hopfield systems could still function well in the face of marked pruning of axonal projections, but that after a certain threshold was passed, a "psychotogenic" disruption of content-addressable memory would be produced.

Methods and Results

Reduced synaptic density and interneuron connectivity was studied by simulating 100 interactive neurons spread out as a 10 × 10 array or "neural sheet." Each simulation was composed of nine different activation patterns stored as memories by the 100-neuron network. Each of the nine activation patterns was derived using a random number generator to determine whether the activation state of each neuron for that memory was 1 or -1. Storage of the nine activation patterns was accomplished using equation (2) yielding synaptic strengths ranging from -9 to 9.

After all of the $T_{xy \rightarrow ij}$'s had been computed, an axonal pruning rule was applied:

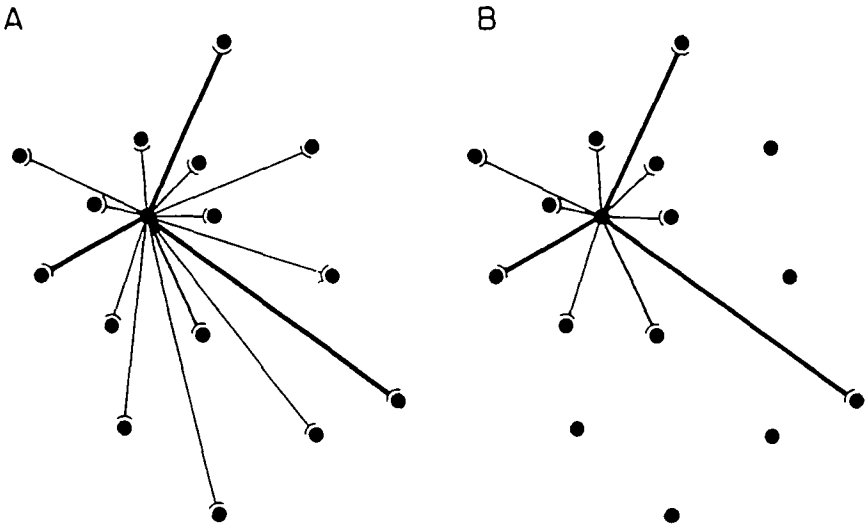
(3) If $|T_{xy \rightarrow ij}| < \hat{p} \times [(i-x)^2 + (j-y)^2]^{1/2}$ *then prune axon* $(x,y) \rightarrow (i,j)$

As the pruning coefficent, $\hat{p}$, increased, more axonal projections were functionally eliminated by reducing their synaptic strengths to 0; among projections with greater axonal length, only those with very robust synaptic strengths were retained. For example, assume that the pruning coefficient was 0.6, and a particular axon traversed a total of eight units (assume the dimensions of the neural sheet to be 10 × 10 units). Then if the absolute value of the synaptic strength achieved by that axon is 0.6 × 8 = 4.8, it will be pruned away—if, however, the synaptic strength is > 4.8, it will be retained. On the other hand, if the axon only traverses three units, then the synaptic strength, in terms of absolute value, need only attain a value of 0.6 × 3 = 1.8 to be retained. This pruning process is illustrated by figure 1; using the earlier analogy of axons viewed as branches of a tree, pruning requires that thinner branches traversing longer distances get pruned away. The principle that only the strongest axonal connections survive, a type of "neural Darwinism," has recently been described by Edelman (1987).

Each of the ten 10 × 10 array realizations stored a unique set of nine, randomly generated memories. Each of these array realizations was then assigned a different pruning coefficient. Larger pruning coefficients resulted in more aggressive pruning. Pruning coefficients ranged between 0.6 and 1.0 and resulted in axonal wiring reductions ranging between 0.72 and 0.92. This figure was calculated by dividing the summed length of pruned away axonal projections by the total amount of axonal "wiring" required by the unpruned system. Corresponding reductions in the total number of synapses ranged from 60 to 85 percent.

After a pruning coefficient has been designated and axonal pruning has occurred, the system is tested for its ability to converge upon the memories that it has stored. For each simulation, startup states 20 and 33 Hamming units away from each of the nine stored memories were chosen. Hamming unit distance reflects the dissimilarity of pairs of activation patterns, and equals the number of neurons whose state does not match when one pattern is compared to the other. Startup states were determined by setting the initial state to match a particular memory, and then reversing the activation state for every third or fifth neuron. If the startup state was generating by reversing the

Figure 1. A diagram of the effects of the axonal pruning rule



Note.—Thickness of axonal projections corresponds to the robustness of synaptic strength from a single neuron to other neurons in the system. Weak axonal projections that traverse longer distances in A are pruned away in B.

state of every third neuron, this would place it 33 Hamming units away from the target memory. If the startup state was generating by reversing the state of every fifth neuron, this would place it 20 Hamming units away from the target memory.

Networks tended to flow into the memory that is nearest, in terms of Hamming distance, to the startup state. Because networks stored complements of the original nine memories loaded into the system as well as the memories themselves, the maximum Hamming distance separating a starting state and a memory was 50 Hamming units; if, for instance, a starting state was 51 Hamming units from a particular memory, it would automatically be 49 Hamming units from its complement. Thus, startup states that were 33 Hamming units from a memory corresponded to a moderate degree of input ambiguity, while startup states 20 Hamming units from a memory corresponded to mild input ambiguity. Since 9 different memories were stored, each of the 10 networks underwent a total of 18 test runs, the first 9 runs when input information was quite "close" to the target memories, and the second 9 runs when input information was "farther away" from target memories.

As described earlier, neuronal states were readjusted in cycles. As opposed to the example in the introduction, this readjustment was accomplished probabilistically. Adding a degree of randomness ensured that the network flowed into its optimum crystalline configuration.[2]

[2]This noise-induced optimization process is analogous to shaking a box of blocks—thereby introducing a certain randomness in their individual spatial configurations—to get the most efficient alignment of the blocks. Randomness was introduced into our systems by readjusting neuronal states on the basis of the following equation:

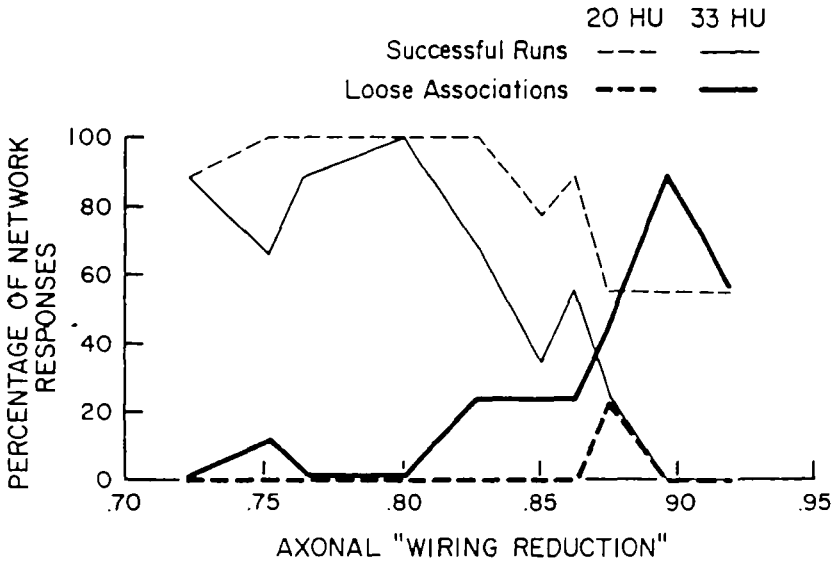
$$(4)\ P_{ij} = \frac{1}{1 + \exp\{(-1/T^*)[\Sigma T_{xy \rightarrow ij}\ \mu_{xy}]\}}$$

Here P_{ij} is the probability that the neuron (i,j) will be turned on, E_{ij} is the synaptic input to neuron (i,j), and T^* is a scaling factor that acts as temperature does in physical systems (for a more complete discussion of this equation, see Hoffman 1987*a*). At very low T^* levels, equation (4) approximates a step function with 0 threshold for summed inputs—similar to that illustrated in our sample network described in the introduction—while at higher temperatures neuronal states readjust with increasing degrees of randomness. For all simulations, T^* was set at 4.

Each network always stabilized by three to five cycles to what will be referred to as the *end state*. Network performance was determined by noting the Hamming distance separating target memory and the end state. An end state three or less Hamming units away from the target memory was scored as a "direct hit." An end state that was 3–10 Hamming units away from the target memory was scored as an "approximation." An end state greater than 10 Hamming units away from the target memory resulted in one of two outcomes: "Generalizations" were end states closest to the two or three stored states to which the startup state were closest—generalizations combined features of the memories which the starting state most closely resembled—while "loose associations" were end states greater than 10 Hamming units away from the target memory that were not generalizations.

Figure 2 summarizes the effects of different degrees of axonal prun-

Figure 2. The effects of varying degrees of axonal pruning on memory convergence



Note.—Pruning coefficients ranged between 0.5 and 1.0. Starting states were chosen 20 and 33 Hamming units (HU) away from each of 9 stored memories yielding 18 test runs per simulation. Successful runs were either "direct hits" or "generalizations." "Approximations" were not included in this graph

ing. Network performance was quite good up until axonal wiring reductions of 80 percent. Beyond this threshold, a marked degeneration of network convergence with a large number of "loose associations" occurred. Of significance is that when startup states were at the 20 Hamming unit level (i.e., input information was not very ambiguous), even those networks that were pruned well beyond threshold were protected to a large extent from loose associations. Most of the pathological responses, even when the networks were quite radically pruned, occurred when startup states began 33 Hamming units away from target memories (i.e., conditions corresponding to moderately ambiguous input information).

A qualitative assessment of network convergence was undertaken by examining end-state activation patterns. Our first prediction was that when overpruned, different portions of the network would flow into different memory configurations. It can be readily calculated that for a 10 x 10 matrix of randomly generated binary numbers, there is a 0.05 chance that a 3 × 4 or 2 × 6 submatrix of identical numbers can be located within the larger system. Thus, we chose 12 neurons in a rectangular configuration to be the smallest neighborhood of significant convergence when end states were compared to target memories. The union of these smallest, significant convergence "patches" was used to determine the overall convergence "superpatch" of an end state and a particular memory. For instance, assume that the comparison of a memory and an end state was as follows:

```
* * * * - - * * * *
* * * * - - * * * *
* * * * * * - * - *
* - * * * * - - * -
- - * * * * - - * *
- * * * * * * - * -
- * * * - - * * - *
* - * * - * * - - *
- - - - - - - * - -
* * - - * * - - * -
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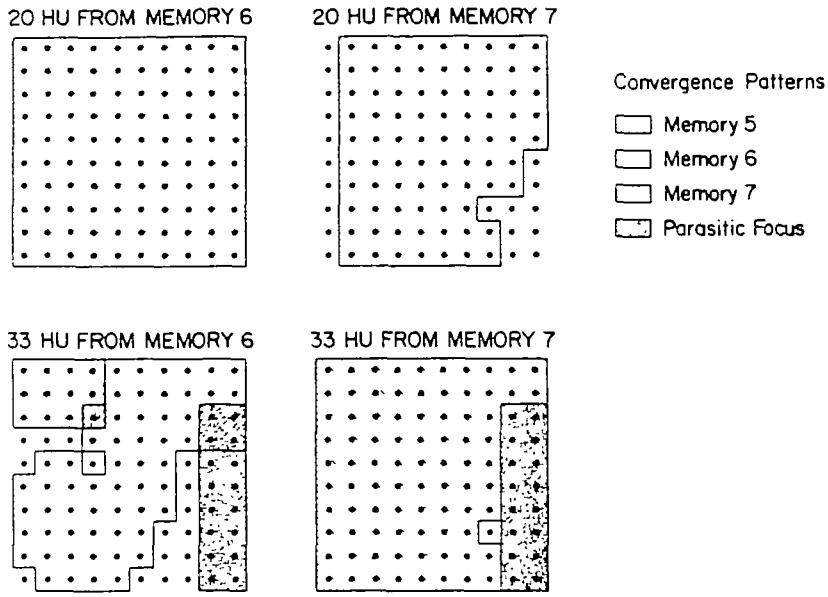
where "-" corresponds to neurons that are in different activation states and "*" corresponds to neurons that are in the same state. There is a large area of convergence by a group of neurons in the left center part of the system. There is a smaller area of convergence in the upper right quadrant, but this would not be included in the overall "superpatch," because its size was less than 12 neurons.

This analytic method determined that overpruning did indeed cause functional fragmentation of networks. Eighty percent of all loose associations showed patches of convergence with different memories (or memory complements) in different portions of the same network for a given run. For different runs of the same network, fragmentation lines (i.e., spatial boundaries between neighborhoods of convergence of different memories), in general, were quite variable. In other words, there were not particular portions of the system that tended to become functionally autonomous. Not surprisingly, when partial convergence to a memory distinct from the dominant convergence pattern of the system occurred, it frequently manifested itself in one of the network's corners; this is where neuronal interconnections are particularly sparse. The size (counted as number of neurons) of memory

convergence "patches" among loose-association outcomes ranged between the minimum of 12 to a high of 87, with a mean of 24.6. Overpruned networks, at times, flowed into a melange of smaller memory shards that did not include even a fragment of the target memory.

Also of note was the occurrence of "parasitic foci." These were localized areas of overpruned networks that tended to lock into specific *nonmemory* activation patterns regardless of the flow pattern of surrounding neurons. Parasitic foci were delineated in the same fashion as memory patches, except that end states were compared to each other as opposed to the original stored memories; a neighborhood of convergence onto a shared nonmemory activation pattern that was greater than or equal to a 3 × 4, 4 × 3, 6 × 2, or 2 × 6 rectangular area was counted as a parasitic focus, and was found for the three most overpruned networks. Figure 3 illustrates the behavior of one overpruned network producing condensations of memory fragments as well as the intrusion of a parasitic focus in the lower right quadrant. Of interest here is that the parasitic focus was once *indirectly* expressed insofar as the lower right quadrant showed increased difficulty in converging onto the proper memory even in the absence of the manifest parasitic activation pattern; this outcome was obtained when the starting state was 20 Hamming units away from the target memory. The mean size of parasitic foci was 30.0 neurons. They were often, but not invariably, induced when different memories, within a local area, shared the same activation pattern. Neighboring neurons outside of the overlapping area then got locked into a pattern that did not reflect any memory,

Figure 3. Outcomes for 4 runs on an overpruned network with an axonal wiring reduction of 0.92



Note—For target memory 6, a less ambiguous starting state (Hamming units = 20) yielded total convergence, while for target memory 7 at the same startup ambiguity, partial convergence was obtained. With increased startup ambiguity (Hamming units = 33), pathological outcomes resulted Targeting memory 7 yielded a local, nonmemory pattern of activation that was precisely re-created by the test run which targeted memory 6. Slavishly re-created activation patterns of this sort were identified as "parasitic foci." The latter test run also yielded a "patch" of memory 5 condensed with a larger "patch" of memory 6

and the entire configuration acquired considerable power in intruding into the overall flow of the network.

Discussion

The functional architecture of the cerebral cortex is largely a mystery. However, there is a growing body of evidence indicating that the cerebral cortex possesses a high degree of interconnectedness and parallelism. Neural information-processing systems of this type most likely share common features in spite of major differences in architecture or individual neuron behavior. Certainly the neuronal network simulations described here are trivially simplistic in comparison to actual brains. However, a likely common feature of parallel-designed neuronal systems—no matter how simple or complex—is that they are vulnerable to functional breakdowns when interconnectednesss is excessively reduced.

These simulations of overpruned parallel-designed neuronal systems revealed three major findings. First, overpruning tended to elicit functional fragmentation with different parts of the network flowing into different memory fragments. Second, reducing the degree of ambiguity of input information tended to protect overpruned systems from pathological responses. Third, under conditions where pruning was particularly extensive; parasitic foci were induced that

intruded into the overall flow of information in the system.

The symptomatic behavior of overpruned systems is congruent with the findings of a number of empirical studies of schizophrenia.

Content-addressable memory simulations can reflect visual perceptual processes by considering each memory to be a gestalt consisting in a bundle of visual features. Overpruned networks often produced condensations of multiple memory fragments in response to ambiguous input data. This behavior models the contamination Rorschach response, that is, fusion of multiple disparate gestalts, that is specific to schizophrenic patients (Holzman et al. 1985; Lerner et al. 1985); Rorschach inkblot stimuli are, in effect, ambiguous stimuli and thus are analogous to network runs when started up at a greater Hamming distance from the target memory. Fusions of multiple, disparate gestalts have also been detected when studying ordinary schizophrenic speech (Hoffman 1986). Thus, the functional fragmentation of overpruned parallel networks seems to model aspects of "thought disorder" in schizophrenic patients.

Matthysse (1974) has noted that pharmacological blockade of the nigrostriatal dopamine system reduces the responsiveness of the basal ganglia to cortical impulses in the generation of motoric action. He postulated that dopamine blockade, at an ideational level, similarly reduces responsiveness to input features that coalesce to form conscious representations. Our simulation data indicated that overpruned systems that "hang fire" until they are quite "close" (in terms of input feature specification as measured by Hamming distance) to actual stored gestalts are able to function successfully. This suggests that dopamine blockade could reduce or eliminate psychotic symptoms due to cortical overpruning by rendering the pathological system more cautious, that is, requiring that the system wait to receive more input data before the system is allowed to make a decision. In short, it may be that a pharmacological intervention can compensate for a "structural lesion" in schizophrenia.

When overpruned, patches of the system at times were parasitically controlled by nonmemory activation patterns that repeatedly intruded into the flow of information. If a similar transformation of the schizophrenic patient's frontal cortex occurred, it would not be surprising if he reported one or more Schneiderian symptoms, namely that he no longer had control of his thoughts. In our model, these parasitically produced activation patterns were not actual memories. The parallel situation in humans would be repeated experiences that have no basis in objective reality and do not cohere with other mental processes.

A review of a number of research studies suggests that schizophrenic hallucinations cannot be differentiated from ordinary, internally generated images on the basis of the sensory qualities (Hoffman 1986). Rather, the distinguishing characteristic seems to be that hallucinations, distinct from normal internally generated images, are experienced as involuntary and out of control of the patient. Parasitic foci are, in a sense, like epileptic foci, but where the firing pattern actually codes for meaningful information instead of random bursting of neurons (Hoffman 1987*b*). Insofar as parasitic foci contain particular, decodable information, it is possible that this information could be expressed as images. These images would be experienced as involuntary since they occur autonomously with respect to other parts of the system, and with alien features since they have not derived from any previous experience; thus, parasitically induced imagery would possess critical features that parallel those of schizophrenic hallucinations.

Larger parasitic foci, moreover, rigidly lock into activation patterns specifying the state of most neurons in the system; this pattern holds relatively independent of any input information. If these larger forms of parasitism altered and controlled belief orientations, delusions could result. In particular, the fact that schizophrenic delusions generally are not disconfirmed by external information—that is, their *idée fixe* quality—is accounted for.

Our overpruned simulations may also shed light on cytoarchitectural findings. Benes et al. (1986), in a post-mortem study of prefrontal cortex in schizophrenic patients and controls, found trends toward reduced neuronal density in layers III, IV, V, and VI, with statistically significant differences noted for layer VI. The primary *receiving* layers in prefrontal cortex of corticocortical projections are layers IV and VI (Goldman-Rakic 1988). On the other hand, layer III is the primary layer of origin of corticocortical projections (Szentagothai 1978). Excessive pruning of corticocortical projections entering and within prefrontal cortex, because of the loss of trophic effects (O'Leary 1987; Thoenen et al. 1987), could induce a secondary diminution in neuronal density in layers III, IV, and VI. Only Benes' findings for layer V—which were not statistically significant—cannot be

conceptually linked to our computer model. Consistent with Benes' findings is that any neuronal loss, according to this model, would not be secondary to a primary degenerative disease of the neurons themselves (such as in Alzheimer's disease), but instead would reflect neurons responding normally to the loss of trophic stimulation.

Another developmental model of schizophrenia offered by Weinberger (1987) assumes that schizophrenia is due to an inherited or perinatally induced neuropathology of frontal areas that is expressed when these areas mature during adolescence. His model, like our own, does well in accounting for the age of onset of schizophrenia. Our computer model is consistent with Weinberger's model if the inherited or perinatally induced neuropathology yields reduced baseline cortico-cortical connectivity. Then normal amounts of developmentally induced axonal pruning could exceed the "psychosis threshold" at the end of adolescence. Along these lines Mednick et al. (1988) have reported a significantly higher incidence of schizophrenia among the offspring of women exposed to the Helsinki A2 virus epidemic of 1957 during their second trimester of pregnancy. This is the time period when layer III neurons of the cortex are generated (Goldman-Rakic 1987); since layer III contains the primary cells of origin of cortico-cortical projections (Szentagothai 1978), a reduction of this cell type due to viral exposure could cause an overall reduction in baseline cortico-cortical connectivity at birth. Unlike Weinberger's model, our computer simulation findings also predict a second type of schizophrenia that does not require preexisting neuropathology but, rather, is secondary to a failure to shut off axonal pruning at the end of adolescence.

The developmental model of schizophrenia that we have discussed is by no means proven; it is able, however, to integrate a large body of research findings and warrants further testing. Of special interest would be electron microscopic study of synaptic density in the prefrontal cortex of schizophrenic patients, as well as physiological methods for detecting parasitic foci.

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