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Concerning Relationships Between Cerebral Blood Flow, Synaptic Pruning, and Early Mental Development in Animals and Humans

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Abstract

Neurophysiological and behavioral observations of rats, primates, and humans demonstrate that the amounts of blood which flow to the sensory and cognitive domains of the brain increase with the degree of environmental stimulation and interaction. These studies provide information on the early rate and extent of development of synaptic architecture and activity in the brain and accompanying increases in metabolic demands together with some evidence for cognitive correlates.

An exuberant growth of synapses is observed in animal brains beginning during gestation and continuing for several weeks to months after birth. The synapse population peaks and then begins a decline which reaches a quasi-plateau in monkeys at about puberty and in humans at five to ten years. The decline continues throughout life but at a considerably lower rate which is apparently related to an aging process. The initial steeper decline is commonly referred to as "pruning" or programmed cell death and is considered an essential part of a learning process by many investigators. Pruning apparently occurs by atrophy which is caused by failure of the circulatory system to deliver a continuing, adequate supply of oxygen and carbohydrate to neurons which are not incorporated into active, synchronously firing aggregates or programmed loops.

It is generally believed that newly formed, unprogrammed synapses begin to fire very soon after formation. However, they do not necessarily attract the trophic factors and blood supply that are necessary to meet the energy demands of sustained firing. At least two feedback processes are known which can help keep programmed cells viable while failing to operate as favorable for unprogrammed cells. (See "Molecular Biology of the Cell", edited by Bruce Alberts et al, Garland Publishing, 1989)
In the first process presynaptic cells which have just discharged are rewarded by a spurt of NGF (nerve growth factor) from their target postsynaptic cells. Programmed firing of aggregates is more likely to stimulate NGF to the participating cells than non-coherent, spastic firing. This process operates according to the "firing rule" which has been stated in the following way:

Each excitation of the target cell tends to consolidate any synapse where the presynaptic axon terminal has just been active and to cause rejection of any synapse where the presynaptic cell has just been quiet.

A possible explanation for the firing rule is that a presynaptic cell which has just discharged a neurotransmitter by exocytosis is better conformed to absorb a consequent immediate release of NGF by the target cell than are other presynaptic cells which have not recently discharged.

In the second process new capillaries are formed to provide nutrient to cells which are firing in a programmed fashion. Apparently they do not form in response to unprogrammed firing. This effect has been observed in mice. Those which are raised in an environment which provides a high degree of stimulation for thirty days after weaning show a 50% greater degree of capillary development than those raised in a standard laboratory environment. They also show corresponding increases in total synapses and in development of superior skills. In addition, PET data reviewed later in this paper do not show the early sharp increase in glucose demand in human infant brains which would provide the energy needed by the sharp early increase in total synapses. The increased vasculature that is ultimately necessary to support an increased demand for nutrient is produced in response to the release of angiogenic factors from cells which need oxygen. In the brain the release or effectiveness of such signals is apparently greater for programmed synaptic firing than for unprogrammed firing.

If the immediate energy requirements for unprogrammed synaptic firing are supplied by catabolysis of a limited amount of local nutrients, only those synapses will survive for which presynaptic cells receive additional nutrient from a continuing supply of blood. The effect of increased NGF, as described in the first process, will be positive but insufficient if adequate supporting vasculature fails to develop. Since adequate vasculature is not initially in place to begin with, it seems likely that an exhaustible
supply of some nutrient other than blood-supplied glucose is initially present in the neonate brain.

Unfortunately, there is a dearth of information on the precise way the increasing energy needs for sustained synaptic activity are met during maturation of the neuronal architecture. If, indeed, the suggested processes are real, the rate of atrophy should compete with the rate of postnatal programming which is presumably proportional to the amount of sensory stimulation received from signals originating in the environment. This view implies that the number of surviving synapses varies with the richness of the environment and that more stimulating environments should produce plateaus in total synapses at earlier ages and at higher levels. It also implies that the slope of the early increase in synapse population is steeper than the slope of the increase in blood demand because unprogrammed synapses produced shortly after birth presumably increase their metabolic needs at a rate which tracks the rate of programming rather than the genetically determined initial rate of synaptic growth. On the other hand, if it is observed that the surviving fraction of synapses tends to be a constant for healthy children, unlike the observations in primates where the environment makes a difference, it would strengthen the argument for pruning as a process which produces a synapse population that is "best" or "most sustainable", a function that is more purposeful than the mere improvement of signal to noise ratios in the cerebral cortex by atrophy of unprogrammed cells.

I look for observations which involve dynamic relationships between the rate of early growth in the synapse population and the rate of growth of blood supply due largely to the energy demands of increasing neuronal activity and synaptic firing. Quantitative data concerning the rate of early growth of synapses, particularly in humans, is quite limited compared with information on the rate of increase in blood flow. The latter observations include measurement of the rate of increase in cerebral vascular development, increases in thickness of the cerebral cortex to accommodate new vasculature, and the resting rate of glucose metabolism in various cerebral domains as measured by PET analysis. In addition, observations of increasing cognitive skills on the same time scale help indicate relationships to rates of neurophysiological maturation.

A comprehensive review of relevant animal studies, particularly with rats, is provided by Greenough (1993). Early work by Rosenzweig et al (1962) showed that portions of the cerebral cortex grew thicker and heavier in animals raised in a complex, toy-filled,
challenging environment than in animals raised in standard laboratory environments. This neurophysiological effect of nurture in a more complex environment was apparently accompanied by a mental effect, an increase in problem-solving ability which had been demonstrated more than a decade earlier. Hebb (1947), Forgays (1952), and Hymovitch (1952) demonstrated that rats raised in this way (here designated EC for environmental complexity) learned mazes and other complex tasks faster than rats raised in standard environments (here designated IC or SC for individual cage or social cage). Greenough et al (1973) confirmed this effect, noting that only 30 days in EC following weaning at 25-30 days of age produced significant effects on the rate of learning mazes. Direct physical interaction with the environment, in contrast with housing within but isolation from the environment, is a necessary condition.

These gross changes in the cerebral cortex are reflected in changes at the level of neuronal structure. Greenough et al (1972, 1973) showed that dendritic length associated with stellate neurons from layer IV of visual cortex grew 20-25% longer than in IC rats. The effect in SC rats was intermediate but closer to IC rats. This difference in dendritic length is accompanied by a difference in synapses per neuron. Turner and Greenough (1985) showed that the number of surviving synapses per neuron in visual cortex increased by 20-25% in EC rats as compared to IC and SC rats. However, the density of synapses did not increase. Rather, the density of neurons decreased, presumably because the volume of tissue was increased by non-neuronal supporting tissue. This explanation was supported by observation of two additional neurophysiological effects by Greenough (1993); one, that capillaries in the tissue increased dramatically in EC rats so that the volume fraction (the fraction of the tissue volume occupied by capillary lumens) rose to 0.0135 compared to 0.009 in SC and IC rats; and two, that astrocytes also increase in EC rats after an initial period of hypertrophy. The increase in capillary volume is about twice the size of the increase in synapse density in the same brain region suggesting that, in addition to meeting the metabolic needs of the new synapses, the new capillaries serve an increased level of neuronal activity.

In summary, these observations indicate that enriched experience increases the thickness of some parts of the cerebral cortex and the number of surviving synapses per neuron, and is accompanied by an increased development of other support components including the capillary density which presumably responds to a rising metabolic demand resulting from increased neuronal/synaptic activity. Greenough (1993) observes that cerebral cortex vascular plasticity is limited to very young rats and that vasculature no
longer keeps up with increasing cortical volume in 2-year old rats. Overall, it appears
that higher levels of experience produce higher levels of regional blood flow in young
rats but that a window closes by two years of age.

Additional data are required to allow a direct comparison of the rate of increase in blood
flow with the rate of increase in synapses. Histological evidence reported by Goldman-
Rakic (1997) indicates that neocortical synaptic density in macaque monkey cerebral
cortex increases to a peak level 30-50% above adult density at 2-3 months of age. It then
decreases gradually to a quasi-plateau at about puberty. Cortical glucose metabolism rates
in rhesus and vervet monkeys (Jacobs 1995) increases somewhat less rapidly than
synaptic density, starting in the neonate at about one-third the 300 day age level
(approximate adult age) and peaking at about 60% above the 300 day level. It then falls to
a quasi-plateau at about the same age as the synaptic density plateau is reached. Thus, in
monkeys the synaptic density and metabolic rate peaks are separated by an interval of
about three months but the plateaus are reached at about the same time.

Huttenlocher's examination (1994) of synapse number and density in the visual cortex in
brain tissue of deceased infants, children, and adults shows an exuberant growth of
number and density of synapses between birth and about eight months of age from a
neonate level at about 30-40% of the adult level to about 80% above the adult level at 6-8
months followed by a gradual decline to the norm, an approximate plateau at
adolescent/adult age. The prefrontal cortex may develop somewhat more slowly and
decline somewhat later.

Chugani (1996) has measured the growth of the glucose metabolic rate in a small
population of human infants who presented with pathologies whose treatment required
PET scans. The data cited are restricted to infants with no complications involving blood
flow to the brain. He looked at several domains in the cerebral cortex. In the visual cortex
the rate rose from about 40% at birth of the value in the adult cortex to a broad peak at 4-8
years at about 40% above the adult level and then declined to a quasi-plateau at 10-16
years. Thus, in human brains there is a separation in time of a few years between peaks
in synapse density and metabolic rate in the visual cortex. The plateaus roughly
 correspond in time although the synapse density plateau may be reached somewhat
sooner.
The difference between the time interval separating the peaks in primates and humans can be attributed to the fact that the programming of the labile synapses in primates is completed sooner on a smaller number of unprogrammed synapses than in humans. It is generally accepted that the maturation of glucose metabolism rates tracks the growing demand for blood in the brain.

An approximation for what might be expected if the previous hypotheses are correct can be provided by a heuristic fit to the synaptic density maturation and glucose metabolism rate maturation data provided by Huttenlocher and Chugani respectively. I hypothesize that the synapse density maturation can be represented by an exponential decay starting, for simplicity, at an approximate peak at 8 months of age, of the form:

\[ R_{\text{syn}}(t) = R_{\text{syn, unst}}(t) + R_{\text{syn, st}}(t) + R^0_{\text{syn, st}} \]

\[ = R^0_{\text{syn, unst}}(e^{-(r_1+r_2)t} + \frac{r_1}{(r_1+r_2)}(1-e^{-(r_1+r_2)t}))(1-e^{-(r_1+r_2)t}) + R^0_{\text{syn, st}} \]

where the values of \( R \) are expressed as ratios of synapses at time \( t \) to the relatively stable plateau at puberty:

\[ R^0_{\text{syn, unst}} = \text{peak value of ratio of unstable synapses at 5 months to the plateau, taken as 1.8} \]

\[ R^0_{\text{syn, st}} = \text{ratio of stable synapses at birth to the plateau, taken as 0.4} \]

\[ r_1 = \text{rate of atrophy of unstabilized, labile synapses} \]

\[ r_2 = \text{rate of stabilization of unstabilized, labile synapses} \]

In Figure 1 the descending solid black line labeled \( r_2 \) shows the curve calculated for values of \( r_1 = 0.017 \) per month, and \( r_2 = 0.016 \) per month. This curve schematically fits the "norm" at the quasi-plateau. Based on the assumption that \( r_2 \) is a variable which depends on the richness of the external environment, additional fits are shown for \( r_2 \) multiplied by 0.5, 2, and 3 respectively.

These descending curves represent the calculated decreases in total synapses with time due to attrition in the original number of unstabilized, labile synapses at a rate given by the sum of stabilization and atrophy rates.
The ascending curves show the corresponding growth of the stable synapse component. The dashed curves define the approximate envelope of Chugani's values for glucose metabolic rates (Figure 2) if his values are similarly normalized to a quasi-plateau in his data at 10-14 years, taken here as 0.42. It can be assumed that part of the spread in Chugani's data is due to the fact that the children in his group probably came from widely variable learning environments and that each child was seen just once. Curves for the unstabilized, labile synapses are not shown but approach zero asymptotically as the total synapses approach their approximate plateaus at complete stabilization.

Although Huttenlocher's data do not show concurrent maturation in all parts of the cerebral cortex, unlike what has been reported for primates, similar fits can be made by adjusting the values of the stabilization rate with sensory domain and even making them variable with time. Variability with time is probably closer to reality than the assumption of constancy which is made here.

If the hypothesis that there is a correlation between the assumed stabilization rates and their variability and the glucose metabolic rates proves to be true, it suggests that children who reach high stabilization plateaus may do so several years earlier than those who reach low plateaus at low stabilization rates. A partial test of the validity of the assumptions involved in this fit would consist of repeated measurements of resting blood flow over a period of years in groups of children exposed to learning environments which vary widely in level of sensory stimulation. Unfortunately, the invasive nature of PET scanning, the only technique presently available for making this measurement, precludes its use in an experimental group of infants and toddlers. More extensive data on synapse density maturation accompanied by data on the richness of associated learning environments would provide an additional test. A program which includes PET scanning with an experimental and control group of primates would be feasible now at some considerable cost but its relevance to humans would remain open to question. Nevertheless, in view of the potential significance of such an experiment to the measurement of maturation process in the human brain, it seems to be well worth undertaking. A positive result would almost surely encourage accelerated development of non-invasive techniques in humans.
When it becomes possible to measure resting cerebral blood flow in infants by non-invasive techniques over a period of months and years, comparisons can be made with the maturation of candidate cognitive correlates. A highly desirable product of such research would be a protocol for the online assessment of the effect of various enrichments in the early learning environment. If early increases in cerebral blood flow in humans prove to be greater in enriched early learning environments than in average or low stimulation environments and can evaluate the effectiveness of different proposed enrichments in controlled settings, various inputs can be evaluated quickly and changes customized to individual needs can be made, although longitudinal studies will undoubtedly be necessary to establish the permanence of initial effects.

REFERENCES


