BLOOD FLOW IN THE BRAIN AND ADULTHOOD AGING OF COGNITIVE FUNCTIONS

by

John L. Horn
Professor of Psychology
University of Denver
Colorado

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The flow of blood through bodily tissues is a direct indicator of the functional activity in the tissues. Oxygen is required for the chemical reactions that define function and each increase in activity demands an increase in oxygen. This demand is met by an increase in flow of oxygenated blood to the tissue wherein activity has increased. Some bodily tissues make greater demands for blood than do others. Blood flow to the neurons of the brain -- the gray matter -- is approximately four times the flow to adjacent support tissues -- the white matter. These remarkable features of physiology have spurred the invention of several methods for assessing neural function by measuring the flow of blood to different regions of the brain.

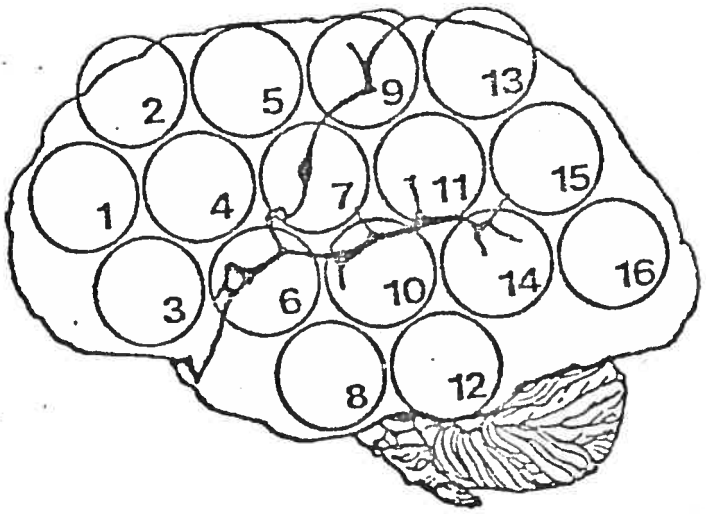
One class of such methods involves putting a standard amount of a radioisotope into the blood at an upstream site and recording the rate at which the isotope passes a downstream recorder that is similar to a Geiger counter. If there is increased activity in the neurons at the downstream site, there is increase in oxygen demand and flow of blood to that site, with the result that more of a standard amount of an isotope marker will pass by a recorder located at that point. Increase in the rate at which an isotope passes a downstream recorder thus indicates increase in the functional activity of the neural tissues that are fed by the blood flow at that site.

An inhalation method of applying this isotope-tracing procedure was used to measure regional cerebral blood flow (rCBF) in the studies of this paper. The radioactive tracer, 133-Xenon, is put into the bloodstream via the lungs by having the subject breath (for precisely one minute) a mixture of 133-Xenon and ordinary air. There follows a period of recording the rate at which the isotope arrives at 32 detector sites in the brain. The detectors are positioned at a right angle to the lateral surfaces of the

head, 16 on the right side and 16 at homologous positions on the left side, as indicated in Figure 1. The measure obtained from the radiation identified with one of these detectors, ISI (initial slope index), is mainly indicative of neural (gray matter) activity occuring in a tubular section of the brain that is about 2 cm in diameter and that extends about 3 cm into the head. The measures at each detector site thus provide information about neural function in the surface sections of the cerebral cortex, not the innermost parts of the brain.

Figure 1

Location of 16 detectors on the left side of the head.
The Rolandic and Sylvian Fissures are also shown.
The dectectors on the right side are located in the same (homologous) way.



The evidence of many studies has now established that ISI measures of regional cerebral blood flow are indicative of both traits and states of individuals. Traits are stable characteristics that distinguish one person from another despite variations in the conditions and circumstances in which people can be found; states are characteristics that vary within a

person and thus distinguish the conditions and circumstances under which a person is observed.

There is evidence that somewhat different things are measured by different rCBF measures. For example, when one becomes engaged in a task that requires concerted attention, blood flow increases at some recording sites, decreases at other sites and does not change notably at still other locations. Also, different central nervous system diseases seem to be associated with different patterns of relatively low blood flow for some of the regional indicators and relatively high flow for others. In general, losses in neural tissues, due to illness or injury or catabolic changes, will be accompanied by drop in blood flow to those tissues. Several behavioral consequences can be associated with such factors.

We were drawn into this line of study by interest in the possibility that different latent variables among rCBF measures might have different relations to adulthood aging and to cognitive changes that accompany aging. We have a substantial amount of evidence indicating aging defects in a class of intellectual abilities known as fluid intelligence (Gf). The aging decline of these abilities is intimately linked to losses in capacities for achieving close concentration, maintaining undivided attention, demonstrating spontaneous alertness, and retaining the facility for encoding information. These deficits of intellectual capacity appear to be associated with particular kinds of neurological malfunctions. Brain damage in an area we well refer to as Ht (to symbolize hippocampus-to-temporal lobe) is accompanied by decline in Gf abilities. The Ht includes the hippocampus, fornix, thalamus, mammillary bodies, parts of the temporal lobe and nearby structures. One might think that neurological damage in these areas would affect all of the capacities that

are thought to indicate intelligence, but this is not the case. Some important classes of intellectual abilities are not at all, or not strongly, associated with Ht injuries that profoundly affect fluid abilities. Moreover, these same abilities do not at all, or do not markedly, decline with age in adulthood. The abilities of crystallized intelligence (Gc), for example, improve over the major part of adulthood and are little, or not at all, affected by the same malfunctions in Ht that are associated with large declines in Gf.

Added to this evidence (indicating different neurological bases for different intellectual abilities) are results suggesting that the parts of the brain that are mainly associated with Gf decline are particularly vulnerable to injuries that can accompany alterations in cerebral blood flow -- injuries that reasonably could occur fairly commonly throughout a normal course of aging.

The arteries supplying the Ht region branch at right angles from the main trunks and terminate in the area as end-arteries. This means that a drop in blood pressure could be critical in the Ht region before it was critical -- or when it was not at all critical -- in regions of the brain that are supplied by blood vessels that branch in the more usual way. Also, the Ht area of the brain lies in a watershed between the territories of the carotid and vertebral arteries. This, too, suggests that the Ht area is more susceptible to ischemic damage than other areas of the brain, because under any conditions of diminution of blood flow, the flow would cease earliest at the branches that are most distant from the primary suppliers. If the Ht region is particularly vulnerable to drop in blood pressure, and over the course of life such drops occur from time to time, then softenings of the brain (infarcts) can develop in those regions that

are most (likely to be) affected by the drops. Indeed, it has been found that infarcts are more common in the hippocampus than in several other parts of the brain.

The peripheral sections of the brain are susceptible to the same kinds of end-of-supply influences that affect the Ht region. These sections, too, are at a distance from main arteries and receive blood via end-arteries. Loss of blood pressure might thus be expected to be particularly damaging to the outer areas of the cerebral cortex. These are the areas in which ISI measures best indicate neural function.

Several kinds of life events can produce a drop in blood pressure. For example, inebriation -- if it is severe enough -- can do this. Indeed, extreme use of alcohol seems to be associated with early "aging" decline of intellectual abilities. Blows to the head, as can occur in sports and work, losses of consciousness for whatever reason, heart attacks and several kinds of illnesses can bring about notable changes in the distribution of blood to the head and consequent loss of neural tissue in vulnerable areas of the brain. Such events occur in the lives of people who are part of the normal population; such events occur as a function of time, which means they would have occurred more commonly in samples of older, compared witlh younger, people. Thus, over the course of what can be regarded as normal aging in adulthood the blood supply to vulnerable areas of the brain can and is expected (on the average, i.e. probabalistically) to drop to critical levels and therefore result in loss of the neurological basis for some intellectual capacities. With the loss of neural tissue there would be corresponding decline in demand for oxygenated blood and decrease in rCBF in the affected areas.

This reasoning and evidence thus suggest three things: 1) aging in adulthood can be associated with decreases in blood flow to the brain; 2) these decreases can be larger in some areas of the brain than in others; 3) the separate rCBF measures indicate such patterns of decreased blood flow and thereby indicate distinct functional organizations in the brain, perhaps reflecting distinct patterns of communication among the neurons. We explored these possibilities by looking for, and verifying the existence of, separate patterns of covariation among rCBF measures, and studying the relationships between such patterns and other variables, particularly aging. Partial least squares (PLS) methods were used in these studies.

The logic of our application of PLS methods rests on an assumption that is fundamental in much scientific work. This is the assumption that an observed set of measurements -- often referred to as a manifest variable -- is only a reflection of variation in underlying, fundamental processes of a system -- the latent (theory) variables. For example, if we estimate the size of vocabulary of each of a number of people, we obtain manifest variable measures that can be indicative of a latent variable known as crystallized intelligence. Similarly, the blood flow measures taken at a particular place on the head might be a manifest variable indicator of a latent variable of neurological function. (Indeed, such a neural function might be the underlying support structure for crystallized intelligence.)

Often it is desirable to "triangulate" in locating a latent variable. The aim in triangulating is to find several manifest variables that covary and thus converge in providing evidence of a process. The identification of crystallized intelligence, for example, rests on the covariation-convergence of several rather different manifest variables. If different manifest variables covary -- i.e., rise and fall together --

there is reason to believe that they are manifestations of the same underlying function. Thus, one can adduce evidence for a function by identifying sets of variables that covary together.

How does one identify sets of variables that covary together? In any sample of subjects there are 630 distinct bivariate covariances among 36 rCBF variables. It can be very difficult to discern distinct patterns of covariation among so many covariances, and if such patterns are identified, it can be difficult to establish that they are more than evanescent findings of a particular search. One needs a set of reliable tools for locating and verifying covariance patterns.

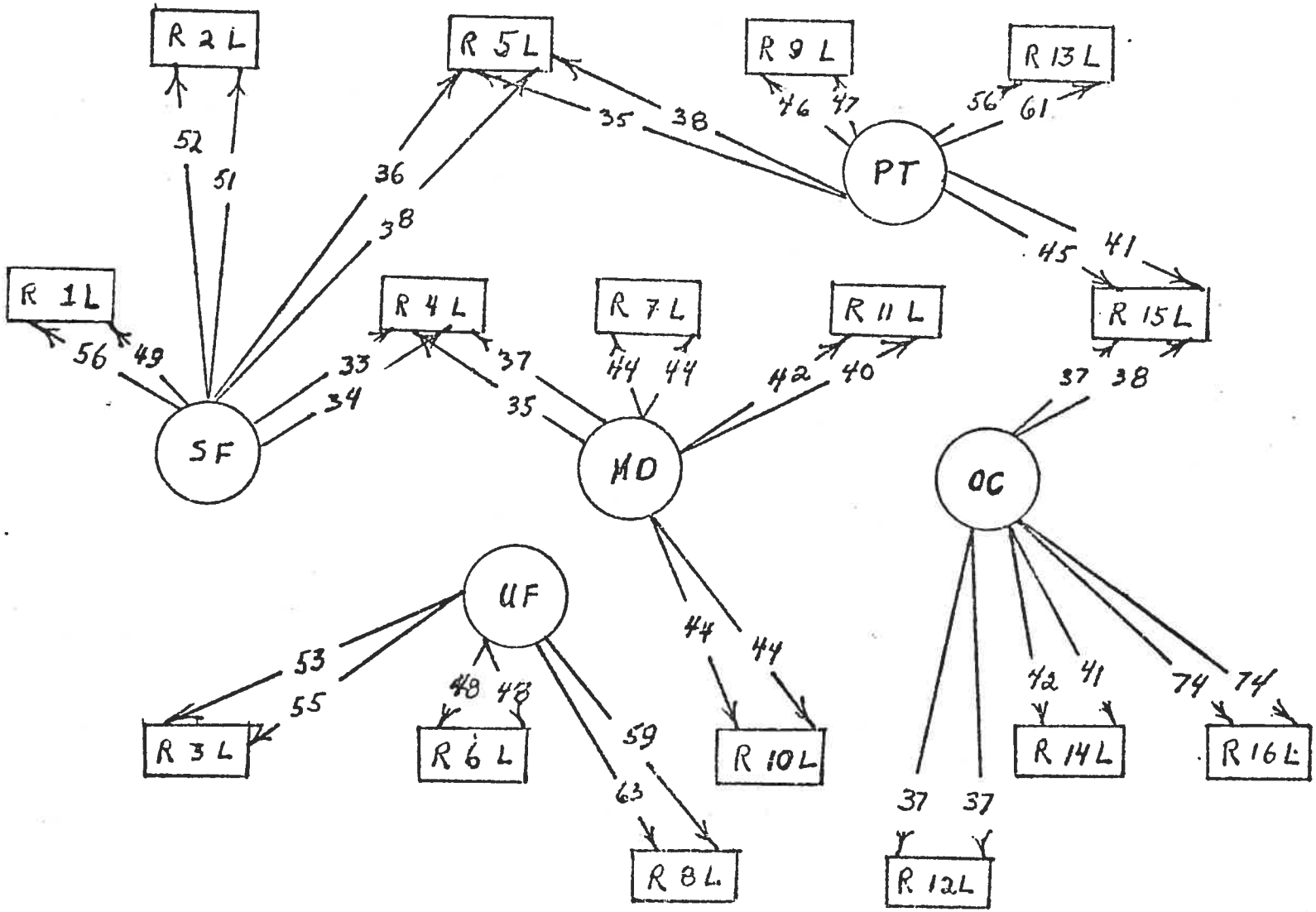
PLS is such a set of tools. It is a series of calculational procedures -- a computer program -- that can be used in either an exploratory or confirmatory manner. When used for exploration, PLS is provided with only very general instructions; the calculational procedures then do an efficient job of analysing the data to locate covariation patterns that optimally (in a least-squares sense) account for the variance of the manifest variables. When used in a confirmatory manner, PLS is instructed to determine if the observed covariances among manifest variables are consistent with a particular mathematical model that the researcher specifies in accordance with theory and hypotheses. The PLS program fits this model in a manner that optimally accounts for manifest variable variances. It then provides mathematical, mensurational and statistical measures of the goodness of this fit.

In the research reported here, PLS was first applied in an exploratory manner in small samples of the available data (891 subjects). The results from these analyses were then used to form hypotheses for confirmatory analyses. Models were fitted under several different conditions for

Figure 2

A MODEL OF REGIONAL CEREBRAL BLOOD FLOW IN THE BRAIN

Rectangles represent manifest variables of the right (R) and left (L) hemispheres. Circles represent latent variables: superior-frontal (SF), parietal (PT), occipital (OC), underside-frontal (UF), and midbrain (MD). Only directed relations (regression coefficients) larger than .3 are given (in the arrows) to avoid clutter.



several different samples of subjects. The results of these analyses led to the conclusions we discuss in the remainder of this paper.

A model that provides a reasonable fit for different subsets of the available data requires 5 intercorrelated latent variables that involve the same configuration of manifest variables on both sides of the brain. Such a model, fitted in the total sample of 891 subjects, is shown in Figure 2.

This model, per se, does not fit different subsets of the rCBF data, but a model of this form provides a reasonable fit in separate samples of the data. Figure 3 has been drawn to suggest how models that fit the data vary from one sample to another.

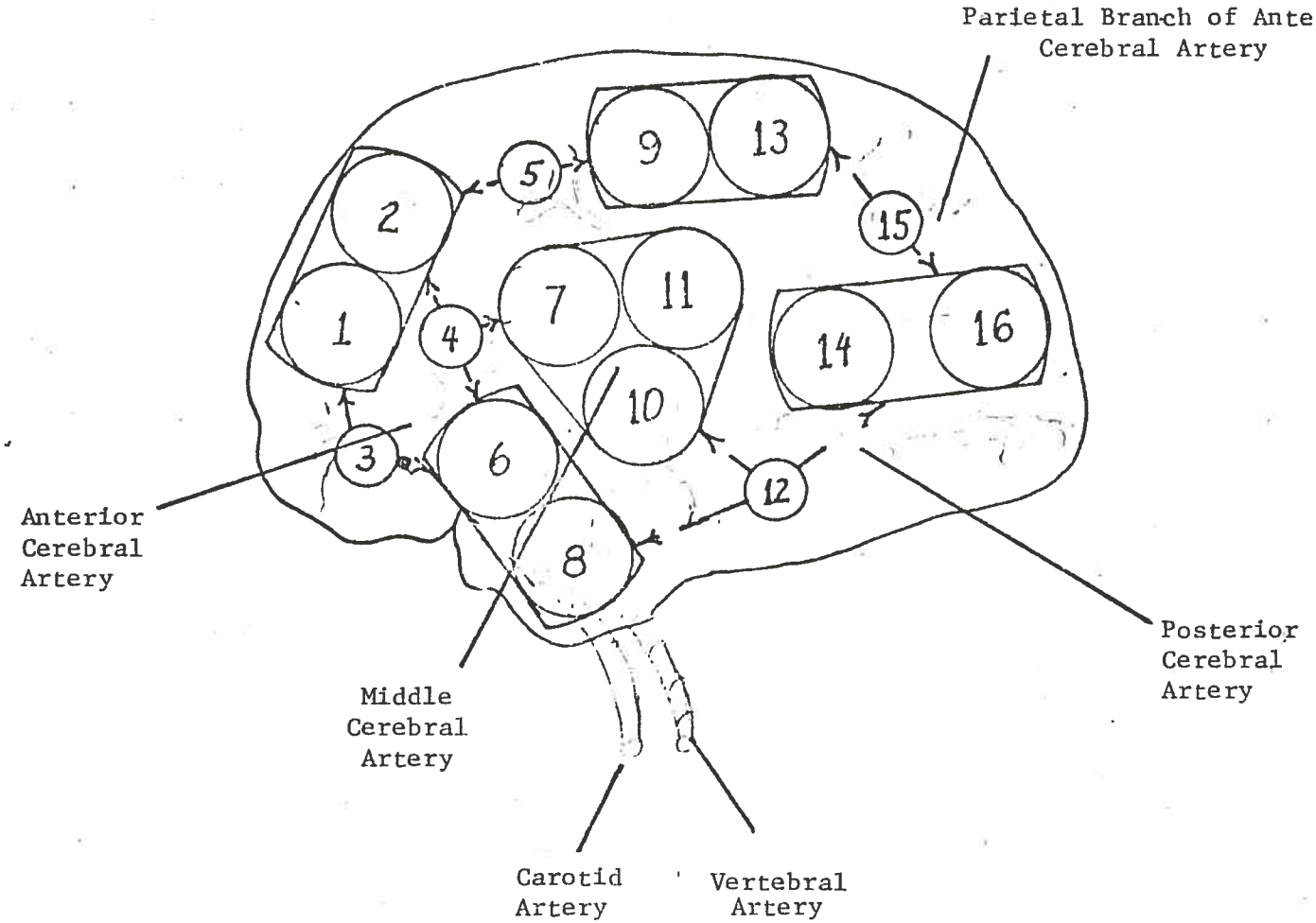
The model of this figure represents a distillation of several different analyses on several different samples of the total sample of 891 subjects. Because the rCBF measures of this figure are representations of what is typical -- i.e., are abstractions derived from the data -- rather than representations of manifest variables, as such, they are (in accordance with current convention) depicted as circles rather than as rectangles. Latent variables are depicted as enclosed groupings of the large circles. It is these groupings, then, that can be interpreted as indicating five different, although correlated, patterns of neural activity.

The relationships between manifest and latent variables vary from sample to sample, but the measures represented by large circles in Figure 3 consistently are highly related to the latent variable of the grouping in which they are bracketed. It's as if each of these variables is near the center of gravity of a particular latent variable function. Each is thus always drawn into the sphere of influence of that function. The small circles represent rCBF measures that are not as consistently involved with

Figure 3

STABLE ORGANIZATION AMONG rCBF MEASURES

The shaded areas represent the "cores" of what seem to be separate functions. The small circles represent "blinker" detectors - i.e. they "blink" in 2 or 3 different difections and, depending on influences operating in particular samples of observations, may mainly align with one or another of the "core" organizations at which they "blink".



the latent variables as are the measures represented by the large circles. It's as if these variables are between the centers of gravity of different functions, and thus can be mainly drawn to one or the other depending on the perturbations produced in a particular sample of subjects and observational conditions. The arrows emerging from the small circles are directed toward the latent variables with which they are usually involved.

For the left hemisphere as well as the right, a model very much like that shown in Figure 3 fits both the between-person and within-person data. What this seems to mean is that neurological organizations are located approximately in the regions of the separate latent variables. The location of these organizations cannot be pinpointed with PLS analyses of rCBF measures, because many influences operate -- in different ways from one sample of data to another. But the bracketings in Figure 3 indicate, roughly, where the organizations are centered.

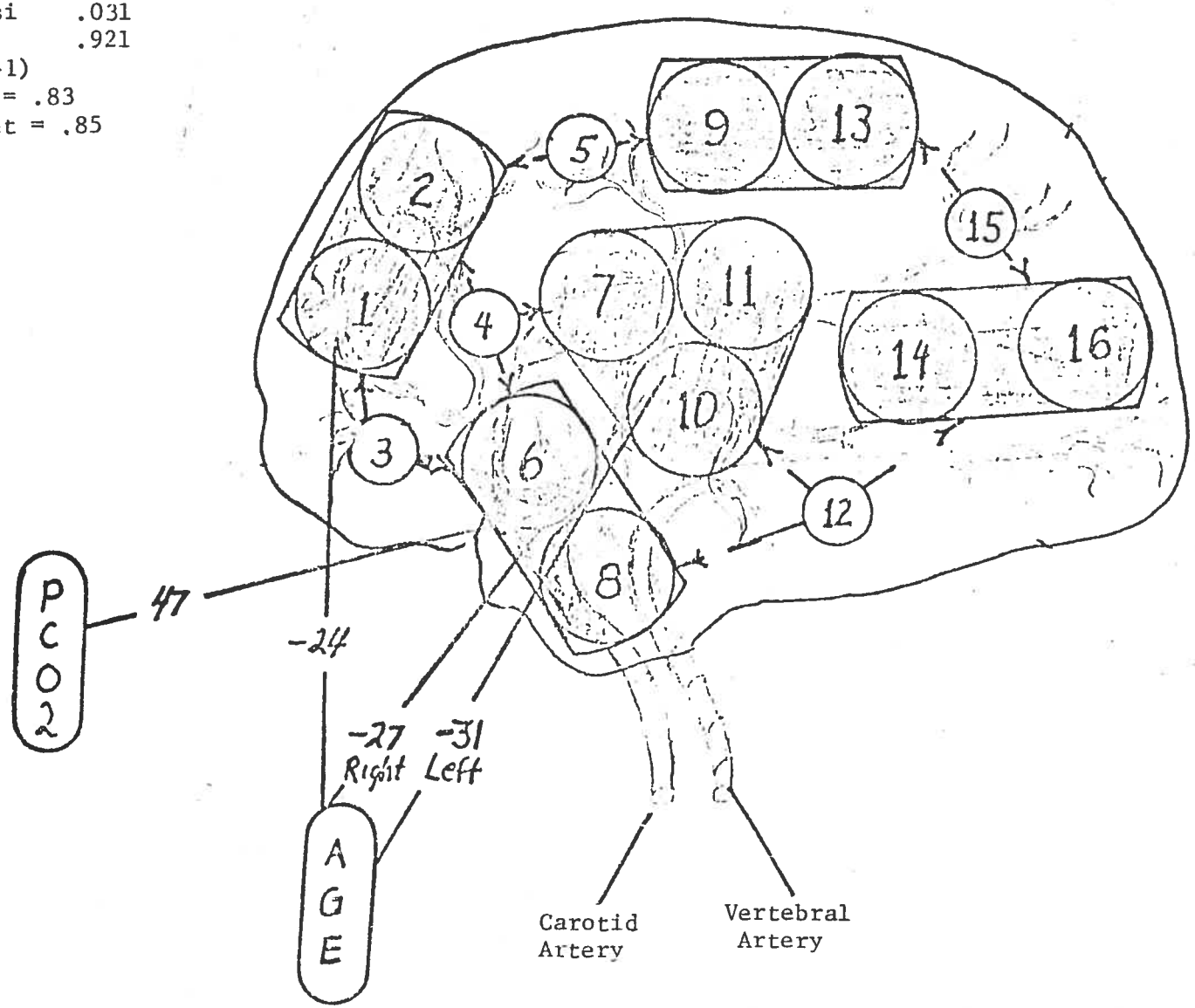
Age in our sample ranged from the early 20's to the late 70's; most of the subjects were between 30 and 60 years of age. All 32 of the rCBF measures had significant correlations with age. The correlations ranged from -.23 to -.58; the negative sign for these coefficients means that the older the age, the lower the rCBF measure. As suggested in Figure 4, however, these age correlations can be described in terms of two of the latent dimensions of the rCBF system. When all the relationships are considered in terms of a model that well represents the total pattern of variable relationships, two latent variables -- SF and MD -- are mainly implicated in the observed correlations between age and the rCBF measures.

The SF and MD latent variables, and the rCBF measures of which they are composed, correlate with a number of behavioral variables in ways that suggest that MD measures an initial, very elementary form of attentiveness

Figure 4

AGE & PCO2-CONTROL RESULTS FROM A PLS MODEL ANALYSIS OF rCBF DATA

Root mean squares:
Residuals: Theta .016
Psi .031
Communality .921
x^2 = 9.97 (n-1)
Tucker-Lewis = .83
Bentler-Bonnet = .85



that progresses, if a problem becomes complex, to an involvement that is measured by SF. For example, if a subject is asked to merely count or squeeze a bulb, there is an increase in the rCBF measure of MD; if the person is asked to solve a matrices problem, however, the rCBF measures of MD first increase and this is followed by an increase in the measures of SF.

These kinds of finding suggest that the neural functions represented by SF and MD are more susceptible to damage -- perhaps damage associated with factors other than aging -- than are other areas of the brain. There is suggestion, also, that the negative relationships of aging with SF and MD are indicative of some of the same aging losses that are associated with decline of Gf.

Could the aging declines of SF and MD be indicative of changes in the Ht region of the brain -- the region for which there is evidence that neural damage is associated with decline in the rather specific set of abilities we have labeled Gf? A problem with drawing this inference is that the rCBF measures are indicative of neural functioning in the surface areas of the brain, not the innermost areas where Ht is located. Only indirectly would decreased blood flow to these inner sections of the brain be associated with the kind of decreased function that is recorded with rCBF measures. MD is adjacent to the Ht area, however. Perhaps because MD is closer to Ht than are other latent variables of rCBF, it is most directly affected by aging deficits developed in Ht. Perhaps, too, MD is an "arouser" of SF, so if (with aging) there is loss in the functions of MD, this is followed in development by loss in the structures of SF.

Finally, too, we should note that MD is a very good measure of the sum of all the rCBF measures (the first principal component). What is seen in

the relationship of MD to aging can be a model compression of the fact that all rCBF measures decline with age.

We are exploring several of the suggestions outlined in this summary.