Functionalexpressionsoftheagingbrain

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In the conventional view, aging of the brain is associated with atrophy vascular abnormalities and loss of volume in hippocampus and amygdala. Cognitively, aging is associated with slowing of processing and memory loss. However, many studies of aging do not examine the cases to exclude demented people. The nutrition and memory in the homebound elderly study (NAME) excluded cases clinically diagnosed as having dementia. Cortical atrophy based on MRI ratings was significantly correlated with vascular disease, white matter hyperintensities, processing speed, and memory but not hippocampus and amygdala volume. Renal function and homocysteine were also associated with cortical atrophy but not with the cognitive variables. In conclusion, brain atrophy of aging in the absence of dementia is related to vascular disease but not hippocampal atrophy. Studies of nutritional interventions should consider using MRI atrophy rather than cognition as outcome.

INTRODUCTION

To illustrate functional expressions of the aging brain, the present article summarizes features of brain structures and functions such as cognition and noncerebral pathophysiology in order to show that, while brain aging is related to cognition and noncerebral pathophysiology, cognition and noncerebral pathophysiology are relatively independent of each other.

The sampling and conceptual problems that limit all human aging studies are well known. For example, the measured intelligence of groups of soldiers entering the military increased for each new group of recruits over the decades since World War I. This type of increase, known as the Flynn effect, is an example of a cognitive birth cohort effect. Over that same time period, the intelligence of an individual tested repeatedly would not have increased. This cohort effect illustrates the difficulty of comparing the cognition of one birth cohort with another.1 Even longitudinal studies that attempt to limit cohort effects are faced with problems of survivorship that truncate any sample. In addition, any population sample is a mixture of individuals aging with and without diseases, such as Alzheimer’s disease, which have discrete mechanisms that may be different from aging. Aging and death are inevitable, but particular diseases are not. For example, in the study of Nutrition, Aging and Memory in the Elderly (NAME),2 the prevalence of dementia increases with age, particularly after the age of 80 years. Yet even at this age, only 40% of the sample will be diagnosed as having a dementia syndrome (Figure 1).

STUDY SAMPLE

The examples shown in Table 1 are based on analyses from the NAME study, a study of homebound elderly in Boston. Of the 1,200 subjects who were interviewed in their homes, 365 agreed to go to the hospital for a more detailed examination. Each was examined by a psychiatrist, a neurologist, and an neuropsychologist. Each subject underwent a magnetic resonance imaging (MRI) scan of the head from which a neuroradiologist made quantitative ratings.

On the basis of consensus diagnosis, the sample was divided into those with and without dementia. The two groups were comparable with respect to education,

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Key words: aging, behavior, physiology
Mini-Mental State Examination (MMSE) score, and verbal intelligence. Their MMSE scores were similar because the subjects with dementia had relatively mild cases, as indicated by their ability to live at home.

**BRAIN CHANGES ASSOCIATED WITH AGING**

The measure of brain structure best associated with aging was selected first. The conventional view is that aging is associated with brain atrophy, smaller hippocampus, and loss of amygdala volume as well as with an increase in white matter hyperintensities and the number of infarcts.3,4

The measure of atrophy was the neuroradiologist’s rating of the width of sulci on the MRI. As shown in Table 2, when both nondemented and demented cases are considered, this atrophy measure correlates significantly with the total cerebrospinal fluid volume, the number of infarcts, the number of white matter hyperintensities, and the volumes of the amygdala and hippocampus. As atrophy increases, the vascular pathology increases, and the volumes of the amygdala and hippocampus decrease. However, if cases of dementia are excluded from the sample, the atrophy measure correlates primarily with cerebral vascular pathology but not with hippocampus and amygdala volume. This has been reported elsewhere.3 Therefore, brain atrophy is used as a surrogate for cerebral vascular pathology to correlate with cognitive and noncerebral pathophysiology. As shown in Figure 2, this measure of atrophy increases with age. The first conclusion, then, is that vascular-associated atrophy correlates with age in a sample that excludes dementia.

**COGNITIVE CHANGES ASSOCIATED WITH THE AGING BRAIN**

Two cognitive measures from the extensive neuropsychological evaluation were selected next. Since the best-replicated aspect of age-associated cognitive change is the slowing of information processing5–7 a measure of cognitive processing speed, the Digit Symbol task, which assesses the capacity of the subject to perform a matching task in 90 seconds, was chosen. Others have shown that white matter abnormalities observed on MRI are associated with attenuated performance on similar tasks of processing speed.5–7 Figure 3 shows that brain atrophy in the nondemented sample is related to slower performance on the Digit Symbol test. In this study, a relatively small amount of atrophy affects this timed task.
The other cognitive task chosen was a memory task that measures the number of words from a list that can be recalled immediately after the list has been read to the subject. This task is not timed. As with the Digit Symbol task, a small amount of atrophy is associated with a significantly reduced capacity to recall words from the list (Figure 4).

Thus, when clinically observed dementing diseases are excluded from the sample, aging is related to vascular-associated brain atrophy, which causes a decrease in performance on timed and untimed cognitive tasks. Others have reported that vascular changes on MRI are associated with low cognitive scores among older individuals.6,8 Since these samples were based on cross-sectional observation, it is possible that cognition could affect vascular brain atrophy or that some third variable could affect both. However, it is most likely that vascular-associated brain atrophy causes cognitive impairment.

NONCEREBRAL PATHOPHYSIOLOGICAL CHANGES RELATED TO THE AGING BRAIN

The NAME study collected a large number of nutritional and pathophysiological measures from which a few examples were selected that showed strong relationships to aging. Others report weight loss follows stroke9 and Alzheimer’s disease.10 Earlier in life, obesity is associated with increased risk for cognitive impairment.11,12 In this study sample, increased weight was associated with less atrophy. An increase in blood homocysteine was found only when atrophy was severe. This association should not be surprising, given the relationship between renal function, which affects homocysteine levels, and brain atrophy (Figure 5). Renal function in this study was measured by the Cockcroft-Gault formula for glomerular filtration rate.13 Confirming the results of another study, a decrease in renal function was associated with increasing vascular-associated brain atrophy.14 Microalbuminuria, a sensitive indicator of renal vascular disease, has been previously shown to be associated with white matter disease.15 It seems reasonable that the pathology in a highly vascular structure, such as the kidney, would be
associated with vascular disease in other structures, such as the brain, especially if both were due to atherosclerosis.

Thus, when clinically observed dementing diseases are excluded from the sample, aging causes vascular-associated brain atrophy, which is associated with abnormalities of cognition and abnormalities of metabolism. It seems likely that pathophysiological abnormalities such as atherosclerosis cause vascular-associated brain atrophy, which then causes cognitive impairment (Figure 6).

The association between brain atrophy and both cognition and metabolic changes suggests cognition and metabolic changes may be related. However, it is possible that metabolic abnormalities could affect cognition through mechanisms other than vascular-associated brain atrophy; therefore, it is worthwhile to examine the association between metabolism and cognition directly. In fact, in many epidemiological studies of nutrition in which subjects are not examined in detail by specialists and do not undergo MRI scanning, cognitive measures are used as outcomes.

If cases of dementia are included in the sample, there is a significant relationship between central processing speed, as measured by the Digit Symbol test, and metabolic variables. Digit Symbol score decreases with elevated homocysteine but increases with improved renal function and with increased energy expenditure. However, if cases of dementia are excluded from the sample, no significant relationship between the cognitive variables and the metabolic variables is observed.

CONCLUSION

Brain atrophy of aging in the absence of dementia was related in this sample to vascular disease but not hippocampal atrophy. Since renal function and homocysteine were associated with atrophy but not cognitive variables, studies of nutrition should consider using MRI atrophy rather than cognition as outcome.

Acknowledgment

Declaration of interest. The authors have no relevant interests to declare.

REFERENCES