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Involutional and Developmental Implications of Age-Related Neuronal Changes: In Search of an Engram for Wisdom

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The changes in neuronal size and number that occur with aging can be viewed from a developmental rather than an involutional perspective. According to this speculative vantage point, age-related neuronal attrition need not lead to intellectual decline and may, instead, represent a progressive fine-tuning of cerebral networks.

SINCE no new neurons are created during the post-utero life of primates, those in existence are particularly prone to accumulate the wear and tear of a lifetime. The occurrence of substantial age-related neuronal attrition is therefore not surprising. Reasonable as this conclusion may seem, its implications, especially as they relate to mental state, are far from clear.

The human central nervous system possesses unique behavioral attributes that could conceivably exert equally unique adaptational pressures upon the process of aging. No other species, for example, is capable of building civilizations. This quintessentially human process necessitates the acquisition of knowledge during an individual lifespan and its transmission to subsequent generations. In most other animal species, biological advantage can be measured by the ability to reach reproductive stage and by the number of offspring that are produced. In humans, it is not far-fetched to postulate that there is also survival advantage associated with successful aging so that the process of information acquisition and transmission can be maximized. Simply stated, individuals who live longer may have a better chance at synthesizing and updating the knowledge of past generations and this may make it more likely that their offspring will inherit information with superior survival value. This information is not encoded in the DNA and cannot be transmitted by procreation alone. Neither can the role of the individual be minimized by pointing out well-stocked libraries that contain all the knowledge necessary for maintaining the process of civilization. Indeed, the millenia of civilizing forces that made writing possible in the relatively recent past must also have depended, in the first instance, on the gradual transmission of acquired information from one individual to another and then from one generation to another.

In keeping with the need for a progressive accumulation of knowledge, the aging of some individuals has been associated with the emergence of a special but elusive enrichment of mental abilities. Many societies, for example, have benefited from gerontocratic modes of governance where an attribute called wisdom, and usually distinguished from cleverness and intelligence, has been identified in old (sen-ate) individuals. This quality is generally considered to be lacking in younger individuals even though they may have the upper hand in vigor, stamina and enthusiasm.

If the assumption is made that the human brain is the principle organ for accumulating and transmitting knowledge, we seem to find ourselves at the brink of a potential paradox: how is it possible to reconcile the age-related deterioration of structure (in the form of neuronal attrition) with the pari passu acquisition of experience, poise, judgement and, ultimately, wisdom?

The roots of this apparent paradox are to be found in current methodological limitations that face the emerging field of behavioral chronobiology. First, we do not yet know how to measure wisdom, a faculty perhaps better characterized by the Piagetian stage-model of development than by psychometric tests of intelligence (e.g., the WAIS). A 20 year old, for example, may never in his lifetime score higher in memorizing a list of unrelated words or constructing block designs but he would not make a good general, labor negotiator, judge or ship's captain. A second and often overlooked problem is how little we know about the dynamic correlates of learning and talent. What, if any, changes occur when we learn how to ride a bicycle, speak a new language or face adversity well? What neuronal variations account for the differences among Newton, Bach and Solon and then between these intellectual giants and those with more modest abilities?

Great strides have been made in the descriptive anatomy of the brain and in the identification of cerebral networks associated with certain realms of mental function. We know, for example, that the limbic system is crucial for learning since damage to this network disturbs the ability to lay down new memories. We have also learned a great deal about the connectivity, chemistry and physiology of limbic pathways. However, we largely ignore how the limbic system changes during learning and how it differs among individuals with vastly different memory abilities. It is therefore not surprising that the emphasis in aging research has also been largely confined to the more static aspects of cerebral networks and how their constituents (neurons, synapses, axons, transmit-

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ters) change in disease states and in the course of normal aging.

Even seemingly straightforward research focused on the relatively more static aspects of cerebral networks is fraught with substantial problems. As workers in this field soon realize, counting neurons is no simple matter (you have to eliminate look-alikes, avoid counting the same object more than once and missing others); measuring perikaryal area is even more difficult (boundaries are not always easy to determine—does one include the dendritic tree, or axonal hillock, for example?); and comparisons across specimens can be quite a formidable task (how does one determine that age rather than fixation, autolysis, and angle of cut is the valid factor?). The presence of such difficulties may explain why the 1955 study by Harold Brody (spanning the age range from birth to late senescence), remains an epic accomplishment that few, if any, have dared to replicate in quite the same fashion [3]. The present comprehensive review by Coleman and Flood [4] is likely to constitute an equally impressive achievement that succeeds in synthesizing vast amounts of apparently contradictory conclusions.

I wholeheartedly agree with the note of caution sounded by Coleman and Flood and I want to add two items of my own. How, for example, does one interpret the size of a neuron ballooned by lipofuscin? Some of my preparations show that perikarya in the nucleus basalis of Meynert may be larger in very old individuals. However, closer inspection shows that most of this area is occupied by lipofuscin granules. Many cortical pyramids accumulate this ubiquitous but mysterious pigment with advancing age. Simple comparisons of perikaryal area may, therefore, be extremely difficult to interpret. Another perennial problem is how to isolate the effect of "age alone" from that of stochastic events embedded in time. In other words, an 80 year old has had more time to have been in fights, smoked and experienced the effects of too much alcohol. When his brain is compared to a 20 year old, which of the differences should be attributed to the passage of time and which to the other variables?

When all of these caveats are taken into account, Coleman and Flood identify a growing consensus that aging is associated with a substantial decline of neuronal number and size in many regions, especially within the forebrain. Although the subject is outside the scope of the Coleman and Flood review, the potential impact of this phenomenon upon mental state deserves further comment.

Embedded within much aging research is the assumption that "more is better." Thus, neuronal attrition is considered a regrettable event that almost certainly provides the structural substrate for the age-related decline seen in many psychological tests. As a counterpoint to this often unstated but commonly implied position, I would like to advance the tentative speculation that age-related neuronal loss and shrinkage (obviously within certain limits) is not that bad.

Let me start this line of reasoning by returning to Brody's study. He showed that cortical neuronal densities undergo a marked decline not only in senescence but also from infancy to adolescence [3]. In language-mediating superior temporal cortex, for example, the count drops by 30% from the age of 2 months to 18 years. The infant has a dazzling repertoire of infinitely flexible babbling but this is hardly more eloquent or expressive than the language of a young adult! This example shows the absurdity of expecting a simple correlation between neuronal number and behavior. Furthermore, and of far greater importance, the Brody numbers are difficult to interpret at the early stages of life because they have not been corrected for rapid shifts in cortical volume. However, basic research in developmental neurobiology has unequivocally established that programmed neuronal death and axonal retraction are fundamental and invariant events in the course of early development [5,6]. Indeed, it is conceivable that some developmental disorders arise because neurons fail to die, and that some types of mental retardation may be caused by the presence of too many neurons. It is, therefore, a legitimate question to ask why neuronal attrition which is described as "developmental" early in life should be called "involutional" when it occurs later on.

Perhaps the timed loss of certain neurons, axons and synapses should be considered as expressions of a unitary developmental sequence that extends throughout the lifespan. In adulthood and even senescence this could represent a process of gradual fine-tuning (or pruning) whereby differentiated patterns of behavior and information processing become established on the basis of proven effectiveness and gradually replace the more global and diffuse activation patterns characteristic of youth. The remaining neural elements of the aging brain are likely to become more specialized as they participate in increasingly more complex neuronal networks, a view that is compatible with the increase in dendritic branching and cortical myelination that is known to continue into late adulthood [4,7]. This process (an enhancement of fidelity at the expense of channel width) is likely to entail a loss of behavioral flexibility and speed but is also compatible with the emergence of wisdom in the face of neuronal attrition. It is conceivable, therefore, that the engram for wisdom contains not only additive but also subtractive processes, at least from the vantage point of brain structure.

In a figurative sense, we might liken the loss of neuronal size and number to the chips that must fall off from a slab of marble so that the underlying sculpture can emerge. Obviously, this process is bound within stringent limits. In extreme aging or in bad aging (e.g., Alzheimer's disease), the falling chips begin to come from the sculpture itself. The important point, however, is to heighten the awareness of an exceedingly complex and almost certainly nonlinear relationship between neuronal mass and mental power, not only in early life but also in adulthood and even senescence. In other words, even if neuronal attrition is an obligatory feature of aging, it is still conceivable that intellectual decline (tested by Piagetian rather than psychometric tasks) is facultative. Indeed, there are cross-sectional as well as longitudinal studies showing that cognitive deterioration is not a universal feature of aging. It occurs when group means are compared but some individuals (approximately a third in most studies) do not show a loss of performance [1].

My intent is not to praise aging but rather to guard against the automatic assumption that neuronal attrition is synonymous with intellectual decline. The stellar examples of Anna Freud, Pablo Casals and Immanuel Kant remind us that senescence is not always devoid of genius. Are these merely expressions of anomalous nervous systems with such reserve power that they remain unperturbed by the attrition of aging, or do they illustrate the more general phenomenon that good aging is a real possibility? Perhaps a concerted belief that good aging is a biological option will refocus research away from involutional features and more towards the mechanisms involved in the establishment and maintenance of that elusive quality called wisdom.

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EDITORAL NOTE

The preceding commentary arrived too late to be reviewed by Drs. Flood and Coleman and was therefore not addressed in the following Author's Response to Commentaries.

Authors' Response to Commentaries

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WE wish to thank the reviewers for their thoughtful comments. We have many areas of agreement and surprisingly few areas of disagreement with this excellent set of commentaries. Our review has been very well summarized by Brizzee. A random sampling of agreements which are not discussed more fully below would include: We agree with Beach and McGeer that no current staining procedure is appropriate for the differential staining of neurons as a general class. However, we must not overlook methods for selectively marking particular neuronal subsets which are currently available. We agree with the importance of age of onset and duration of disease, as suggested by Iverson, Arendt and Bigl and by Scheff. In a large enough sample it should be possible to conduct an analysis which would distinguish between these two variables.

A number of commentaries have suggested addenda to our manuscript which we gratefully accept. The additions by Ball, Beach and McGeer, Mann, Sapolsky and Scheff to our list of considerations in the design and interpretation of studies of the aged and AD brain create a combined set of criteria and considerations that could contribute to the definition of standards for such studies. The number of commentators who addressed this area indicates a widespread concern for this issue which can only be beneficial. Although some of the list of design and interpretation criteria are specifically directed at morphological studies, we wish to em-