A SHORT STUDY ON THE AGING PROBLEM & ITS EFFECTS ON THE BRAIN

PREPARED BY:

SENIHA ESEN YUKSEL

CVIP Lab
University of Louisville
Electrical and Computer Engineering

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ABSTRACT

As people get older their brains encounter numerous changes like decrease in the total brain weight & volume, cortical thinning, gyral atrophy, widening of sulci, expansion of ventricular volume and neurological disorders. The first part of this survey paper gives the basics of the brain to understand the relevant papers and in the second part the studies done on the brain for the aging problem are explained.

Researchers have looked to the brain atrophy from several views. Some looked for specific parts that undergo atrophy, some tried to find the volume of gray matter and white matter, or measure the cortical thickness to observe the changes in the brain during aging. However, due to the complexity of the segmentation process in brain, the results are somehow conflicting and a general view of which part is most affected by age is not determined.

In the aging problem part of this survey, the difficulties in the segmentation process are listed. Then some study examples are given. The first study is an example of the studies on the specific parts of the brain, namely the cerebellum and brain stem. The second topic covers the segmentation and quantification of gray matter and white matter. Gray matter studies are also divided to two groups. One group of studies of gray matter looks at the gyrification problem and tries to find out if more folding occurs by age in the brain i.e. if the curvatures will increase or not. The second group of studies on gray matter focuses on the cortical thinning and tries to determine the distance between the gray matter and white matter. These papers mainly report that the gray matter decreases by age. A following study reports that both gray and white matters are decreasing in aging, and the final study states that it is only the white matter that contributes to the brain atrophy.

At the end of this survey, there is a part on the diseases of brain that will benefit from the aging studies. Aging studies will allow these diseases to be differentiated from the normal aging process and get diagnosed in the early stages.

INTRODUCTION

Aging process comes with its effects like gray hair, wrinkled skin, brittle bones accompanied by functional and structural impairment, discomfort and suffering. The idea in the studies of aging is to take it as a disease and try to diagnose and cure it before it is too late. So the studies are going on in cellular or anatomical levels, but the question how early the morphological changes begin and which areas are more vulnerable to these changes still remains a problem.

Studies have shown that aging makes some visible changes also in the brain. Thus the importance of cerebral cortex in various motor and cognitive functions has drawn the attention on this subject. Moreover, if the normal aging process can be understood, the deviations from the normal brain structures will allow us to detect diseases which affect the brain like dementia (for ex. Alzheimer) or multiple sclerosis in the early stages!

This study covers the studies of aging on the brain. However, still remaining as an unsolved problem, many studies have shown contradictory results because of the difficulties of the problem and many studies have evolved in time with the advancements of the technologies. Still, a general conclusion about the effects of the aging on the brain can be reached. In the rest of the report, several of the methodologies applied will be discussed to give an idea to the reader about the problem and the possible solution methods. To be able to understand the basic concepts about the brain, the following part is a short summary of the brain basics.

BRAIN BASICS

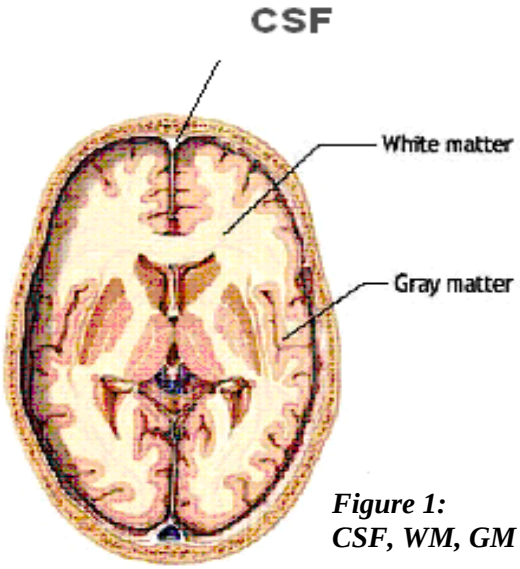

Figure 1: CSF, WM, GM

- "The human **cerebral cortex** is a thin folded sheet of gray matter that lies inside the cerebrospinal fluid (CSF) and outside the white matter of the brain." [1] This thin sheet of gray matter contains 80% of the neurons of the central nervous system and it measures only 1.5mm-4.5mm but its extent reaches 4000cm^3 due to folding (gyrification) of the brain [2].

- **Gray matter** (i.e. cortex) contains nerve cell bodies. It is called gray because of the gray nuclei in the cells; however it appears pink in the living tissue as in figure 1. Gray matter loss occurs due to the decrease in the size of large neurons rather than a notable decrease in the number of neurons

- **White matter** contains lots of nerve fibers that are sheathed in a white fatty insulating protein called myelin. Likewise, white matter loss occurs due to the myelin and axonal destruction.

- **Cerebrospinal fluid** (CSF) is the fluid that surrounds the central nervous system and its volume is between 100 and 140 ml in adults. [3]

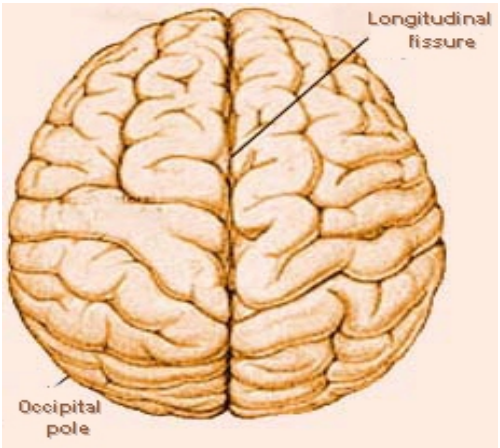

Figure 2: Longitudinal fissure dividing the brain into two hemispheres. (Image taken from [4])

- The folding of the brain is called **gyrification**.
- **Gyrus** is a bump on the cortex (pl: gyri)
- **Sulcus** is a groove (cut) on the cortex (pl:sulci)

- Longitudinal fissure divides the brain into two hemispheres as in figure 2. Each hemisphere consists of 4 lobes: Frontal, temporal, parietal and occipital. These lobes are shown in figure 3.

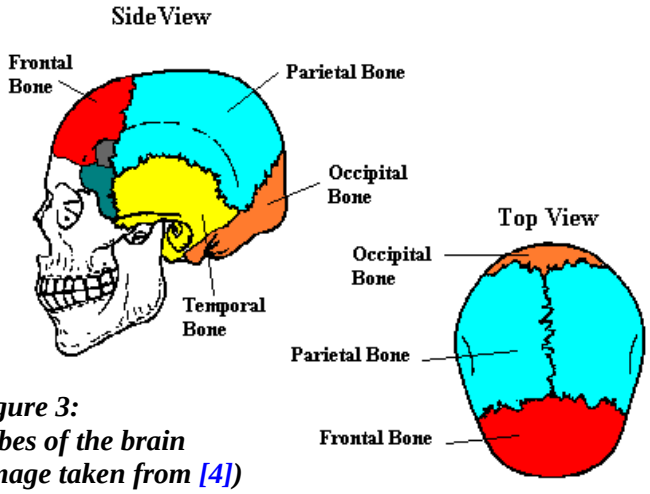

Figure 3:
Lobes of the brain
(Image taken from [4])

- **Frontal lobe** is associated with thinking and planning,
- **parietal lobe** with pressure/pain/ touch/taste senses,
- **occipital lobe** with visual information and
- **temporal lobe** is associated with hearing and memory.

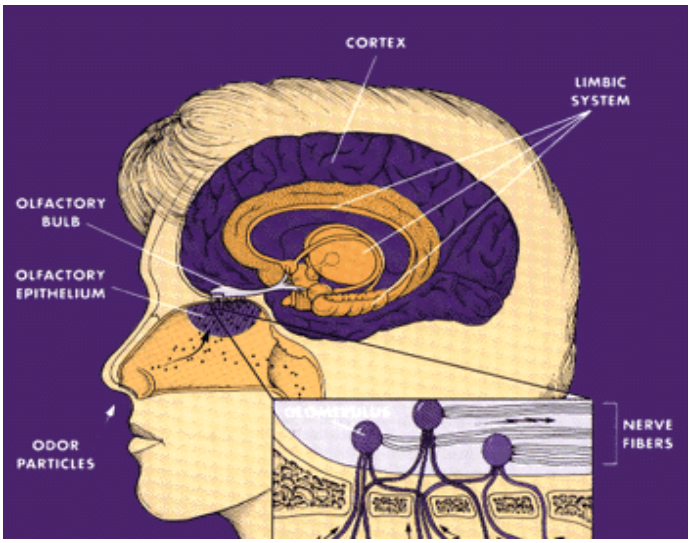

Figure 4: Cortex and limbic system
(Image modified from [5])

- On the medial surface of the temporal lobe there is called the limbic system.
- **Limbic system** (shown in figure 4) consists of three structures: olfactory cortex, amygdale and hippocampus.
- **Hippocampus** is involved with the formation of long term memory. Therefore it is one of the regions under interest for the aging problem.

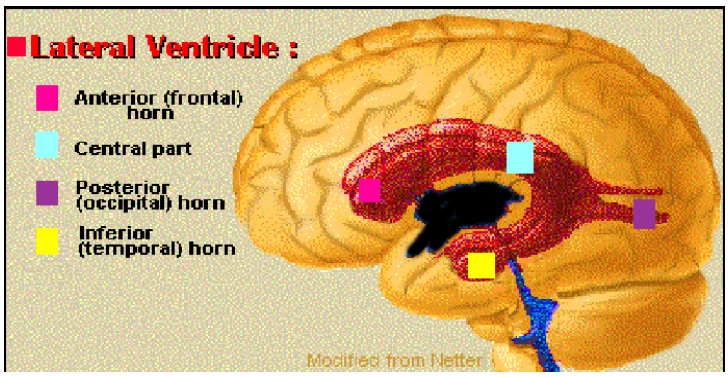

Figure 5: Ventricles of the brain
(Image modified from [6])

- If the brain is cut in cross section, four cavities can be seen in it as in figure 5. These are the four **ventricles**: Lateral ventricles, 3rd ventricle and 4th ventricle.
- The marked parts in figure 5 are the parts of the lateral ventricle.
- The black part in the middle is the 3rd ventricle
- The blue part down the image is the 4th ventricle.

AGING PROBLEM AND ITS EFFECTS ON THE BRAIN:

Until the 1984's, it was thought that the aging process is related to the loss of neurons in the brain. In fact, Brody's group [7] suggested a 100.000 neuron loss daily resulting in 19.7% loss at the age of 80. Conversely, with the advancements of neuron counting techniques, Terry *et al.* [8] found out that there is not much age-related neural loss in the cortex. There is some small decrease however, which has been explained as the cortical thinning or as the structural changes in neurons as they lose their dendritic trees and spines with age in [9, 10]. Wong [9] reviews the structural (dendritic loss, shrinkage of brain), neurochemical (reduction in the level of neurotransmitters and their receptors) and functional changes (sleeping cycle, learning and memory) in the cerebral cortex.

After it was found out that there isn't much neural loss in the brain, the studies had a tendency toward working on the specific parts of the brain that are more likely to get affected by the aging process like the frontal and temporal lobes as they take part in the memory and learning; or the studies worked on the gray/white matter losses, which could be the most likely reasons for the very apparent brain shrinkage/weight loss observed in the clinical studies.

Shrinking of the cerebral cortex (i.e. GM loss) is the most striking feature of aging and it has been shown with MRI studies. Individuals over 60 years old have 17% lighter brains than of young adults [9]. It is believed that the GM loss occurs due to the decrease in the size of large neurons (rather than a notable decrease in the number of neurons). On the other hand, white matter (WM) loss occurs due to damage of myelinated fibers with age [8].

However, WM and GM losses are not the only age related changes. Review of literature shows that the effects of aging have been investigated on specific brain regions such as corpus callous, hippocampus, frontal and temporal lobes and cerebellum [10]. Although these specific brain regions were also found to get affected from the aging process, it is not easy to specifically determine and segment those specific regions automatically from each brain. Thus white matter (WM), gray matter (GM) studies have found more attention.

On the other hand, a reliable segmentation of the cortex and thus quantifying GM and WM is not a trivial task either. The problems with this segmentation can be summarized as follows:

1) Partial Volume Effect: Partial volume effect is where multiple tissues contribute to a single pixel or voxel resulting in a blurring of intensity across boundaries. The partial volume effect is due to the finite resolution of the imaging scanner. The resulting intensity of such a pixel is a weighted average of the intensities of corresponding to the different tissues present [11]. The fuzzy boundaries in the brain lead to fuzzy boundaries between the WM, GM and CSF. Partial volume effect can be reduced by decreasing the voxel size and application of sub-voxel techniques can help warrant meaningful results.
2) A problem in GM applications is the buried cortex where edges of gyral crowns touch one another and the inside is filled with CSF so the surface rendering programs cannot distinguish the folding and count CSF as gray matter [12]
3) Veins and nerve fibers connect the brain to the other structures and making it difficult to place a boundary between the gray and white matter. Thus these structures may contribute to either the WM or the GM in most cases. Peters *et al.* [13] gives a solution to this fact by examining the tissue sections from the same brains that has been scanned.
4) All MR imaging protocols are sensitive to inhomogeneities in the magnetic field so these inhomogeneities should be corrected to obtain comparable values across brain regions.
5) The preservation of the form of the brain is important especially for surgical purposes and methods like isosurface cannot preserve the topology [1].

In the next parts of the report, one example will be given for a specific region segmentation to give an idea to the reader about the difficulty of this task. Then several papers with GM/WM studies will be discussed. And at the end, a small part on the relation of aging and brain diseases will be given to understand the scope and aim of this aging research area.

REGION SEGMENTATION: CEREBELLUM ANALYSIS

Luft *et al.* [14] investigate the age related changes in the cerebellum and brainstem. Brainstem is the portion of the brain that connects the spinal cord to the forebrain and cerebrum. The results show that the brain stem stays stable with age whereas the cerebellum shrinks with age (vermis is affected most, then comes medial hemisphere, lateral hemisphere is not affected).

First the brainstem is segmented then the cerebellum. Both segmentations are composed of three steps. First the structural boundaries not defined by different signal intensities are manually traced. Second contrast-defined boundaries are automatically segmented using a region-growing algorithm in three dimensions. Finally, volumes are calculated considering partial volume effects at the edge of the segmented structure. For the structural boundaries of the brainstem anatomical landmarks and planes are used to make the process automatic. For the cerebellum, the boundary was redrawn manually on every image. The procedure to segment these regions is shown in figure 6.

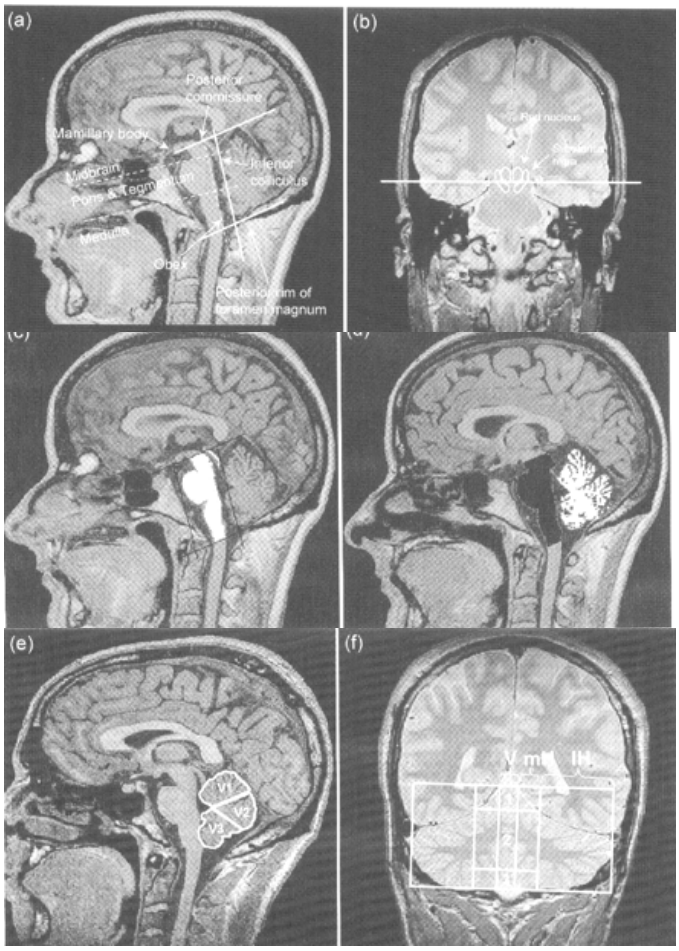

Figure 6: *Landmark-based pre-segmentation and automated region-growing-based segmentation of cerebellum and brainstem are shown.*

(a,b) Several planes were adjusted for two landmarks to define the boundaries and regions in the brainstem.

(c,d) Region-growing-based segmentation identified the full delineation of brainstem and cerebellum.

(e,f) A three-dimensional lattice was used to subdivide the cerebellum into 11 regions. V1, V2,V3 is the Vermis 1,2,3; lH: lateral Hemisphere, MH: Medial hemisphere

(Image taken from [14])

GRAY MATTER WHITE MATTER ANALYSIS

As it can be seen from the previous study and from the similar others where effects on aging are investigated on specific brain regions, the discrimination of these regions and making automated decisions is difficult. To be more reliable and applicable, aging studies are better be applied on the whole brain. Since gray matter and white matter are highly included in the brain and available to distinguish through MR imaging, quantitative analysis of GM and WM has been found to be applicable.

Yet, the segmentation of gray matter and white matter is not an easy task because of the reasons given in the previous parts; therefore conflicting results exist in the quantification of GM and WM. Some studies found the GM to have more importance in aging; some stated WM has greater importance. Several of the researches done up to now will be reported in the following sections to give the reader a view of the research, but a conclusion on aging has not been reached. Below is some of the approaches to the aging problem, the first approach takes the problem as the thinning of the cerebral cortex, which is the decline in gray matter, the second study finds that both gray matter and white matter are important in the aging, and the third study suggests that it is only the white matter which is changing.

1) Gray Matter Studies: Gyrification and Thinning of Cerebral Cortex

Gray matter studies can also be divided into two parts: thinning of the cerebral cortex in aging and gyrification. Cortical thickness is the distance between the gray/white boundary and the outer cortical surface. Salat et al [15] and Kruggel *et al.* [2] give methods to measure the cortical thickness, but in [2] the method is not applied to the aging problem. Magnotta *et al.* takes the problem as a gyrification problem and tries to measure the sulcal and gyral curvatures and also the cortical thickness [12]. These methodologies will be briefly discussed.

Gyrification:

"The increased degree of folding in the human brain is believed to reflect a need to increase its surface area (and consequently its functional capacity) in response to evolutionary demands" [12]. Therefore, quantitative measurements of gyrification can provide important information on aging. The study of Magnotta *et al.* [12] is the first study to examine the changes in sulcal and gyral shape quantitatively.

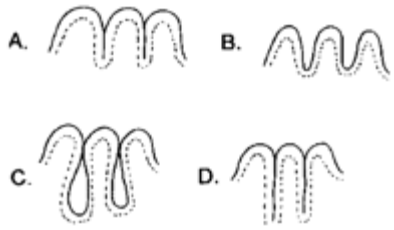

Figure 7: Buried Cortex problem [12]

The main problem in measuring the gyrification is the **'problem of buried cortex'**. That is, the edges of gyral crowns touch one another and the inside is filled with CSF. The surface rendering programs can distinguish a and b in figure 7, but they will fail to detect atrophy when GM pixels touch one another (c) or if there is a deep folding due to high gyrification (d).

Magnotta *et al.* [12] solve this problem by introducing erosion to the entire brain surface so that the gyral crowns don't touch each other. Then GM and WM are segmented by fuzzy and sharp classifiers, and a cortical isosurface is created for the measurements. Then the curvature measure is calculated which determines if the triangles are convex of concave. The convex (positive) values represent gyri, concave (negative) values represent sulci. The curvature measure is the average over all j of $|ji|\cos\theta.e^{-|ji|^2}$ where i and j are the centers of the neighbor triangles and θ is the angle between the normal to triangle i and the vector from i to j. Then surface area is calculated as the sum of the areas of the triangles. The distance between each triangle and GM/WM interface gives the cortical thickness.

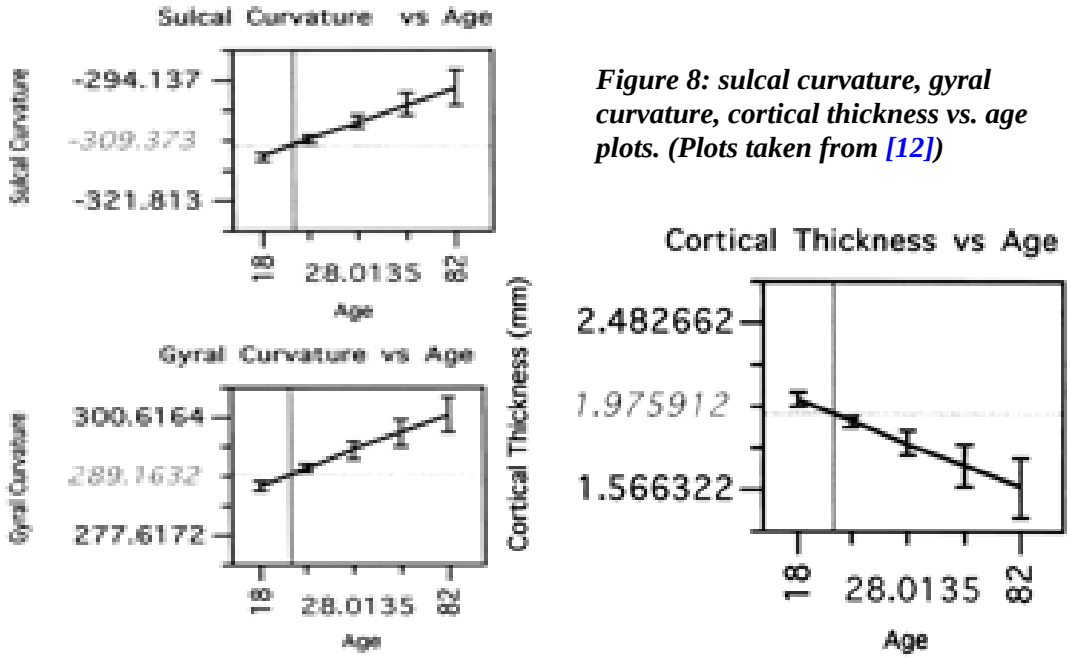

Figure 8: sulcal curvature, gyral curvature, cortical thickness vs. age plots. (Plots taken from [12])

As seen from figure 8, "the results of this study indicate that the sulcal curvature index becomes increasingly more negative, reflecting a flattening and opening up of the sulci; the gyral curvature index becomes increasingly more positive, reflecting a narrowing of the gyral crowns and a sharpening of their curvature; and the cortex becomes progressively thinner." [12].

Thinning of the Cerebral Cortex:

Although the previous study also calculates the cortical thickness, results are not very satisfactory. Another paper that calculates the cortical thickness for the aging problem is [15] and it uses the method of [16].] Dale *et al.* [16] introduce the first complete, automated procedure to make cortical analysis. In the segmentation process of [16], the sub-cortical regions (extensions of GM) are cut out, then white matter is extracted by the use of connected components and the resulting volume is deformed to form the GM/WM surface. But this surface deviates from the spherical shape so these topological defects are manually corrected. Using this method, Salat *et al.* [15] find that the global cortical thickness and global cortical volume declines by increasing age. However, the paper also indicates that "cortical thickening" was also found in some regions, especially in regions of common MRI signal loss and artifact.

Xu [1], Kruggel [2], Zeng [17] also give automated methods but they are not applied to the aging problem. In [17], a level set method with coupled surfaces is used to segment both boundaries in a single step. In [2], intensity in-homogeneities are corrected by adaptive fuzzy segmentation algorithm and the background is regularized by a partial differential equations system. Then marching tetrahedra algorithm (a method where triangulated surface meshes are used) is used to compute the surface of the WM and then by deformable models an improved model of WM is obtained. By projecting a vertex of GM mesh onto the triangles of WM mesh along its plane normal, the cortical thickness is calculated. To find the sulci correctly, morphological operations are applied on the WM segmentation, the deepest point is found by calculating the distances and a region growing algorithm is used to these deepest points to actually determine the sulcal sub-regions. The problem of this method is in the intensity correction where the small areas of high thickness values often correspond to segmentation errors and the results are different than [17].

2: GM and WM both matters in aging:

Ge *et al.* [10] is one of the recent studies which supports that it is not only the GM but also the WM that contributes to the brain atrophy. It is reported in this paper that the %WM decreases in a quadratic fashion with a greater rate in the adult midlife and %GM volume loss appears as linear function of age throughout adult life. Therefore the paper claims that the quantitative analysis of %GM and %WM volumes could improve our understanding of brain atrophy due to normal aging. In this paper GM, WM and intracranial space volumes were each identified by as individual three dimensional fuzzy connected objects according to their "affinity", "fuzzy adjacency" and "hanging togetherness".

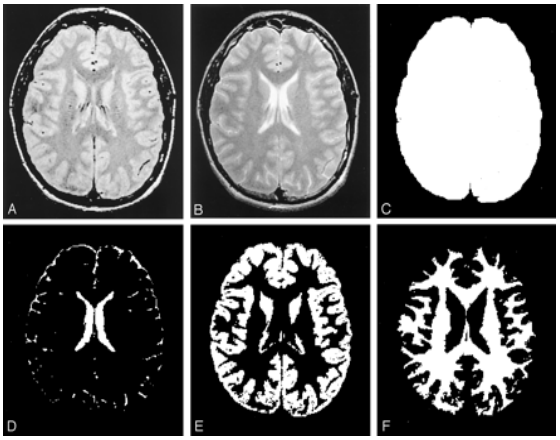

Figure 9:

A) Original dual-echo FSE proton density-weighted image.
B) T2-weighted MR image.
C) Total intracranial volume image.
D) CSF volume image.
E) GM volume image.
F) WM volume image

(Image taken from [10])

To predict %WM and %GM as quadratic functions of age, least-squares regression was implemented as shown in figure 10. Since the brain atrophy was dominated by the changes in WM (note the increased decrease in b after middle ages), the paper reports that the changes in WM can be considered as the beginning of aging.

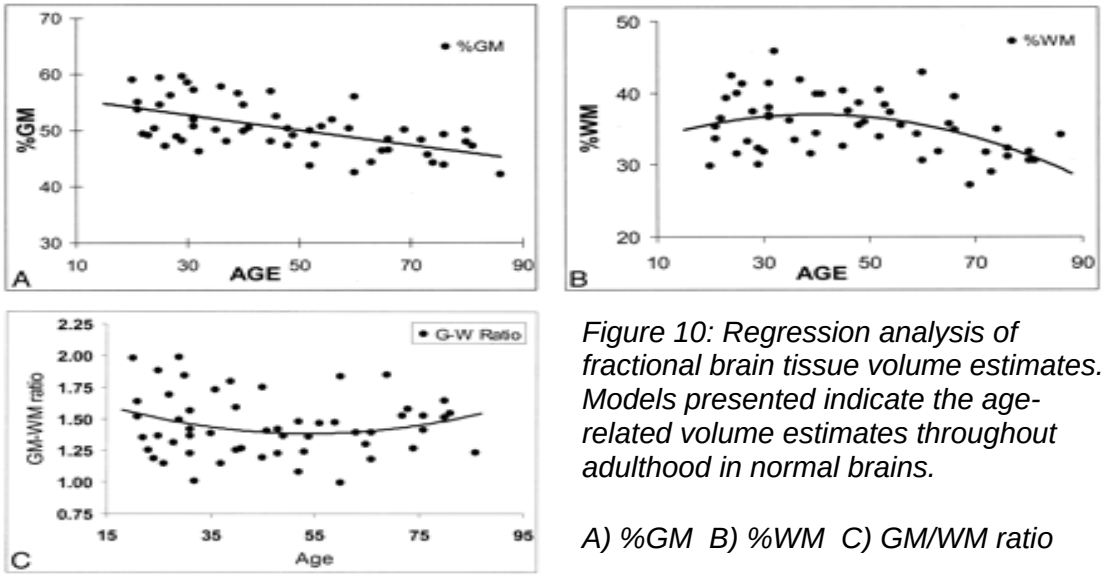

Figure 10: Regression analysis of fractional brain tissue volume estimates. Models presented indicate the age-related volume estimates throughout adulthood in normal brains.

A) %GM B) %WM C) GM/WM ratio

3: Only WM matters in aging:

Peters *et al.* [13] explains the conflicts in many of the papers as segmentation errors & partial volume effect. Thus, especially for the lower layer of the cortex where there is an intermixing of nerve fibers and neuronal cell bodies, this study examines the tissue sections from the same brains that have been scanned. Also the partial volume effect is reduced by decreasing the voxel size to 0.7mm (note that previous studies used 1-1.5mm). Therefore the paper ascertained that the gray/white border in the MRI slices corresponds to the border identified in Nissl-stained histological sections of the same brain

The results indicated no evidence of loss of gray matter but there was a significant loss of white matter with an accompanying decrease in ventricular size. So this study supports the fact there is no or little neuron loss with age and that the loss is the loss of myelinated nerve fibers. It also reports that the WM decrease is greater in the frontal lobes, and whether the WM loss is due to the neural fiber loss or due to the small lesions occurring in the white matter, these changes in white matter could result in a disconnection syndrome and contribute to the cognitive decline in normal aging. Therefore the report suggests that if alterations in myelin and myelinated nerve fibers could be decreased, than some of the cognitive decline associated with normal aging might be retarded.

AGING AND DISEASES:

It is important to know and understand the symptoms of the diseases that occur or show their effects on the brain to separate them from the aging process. Moreover, if the normal aging process can be solved, the deviations from the normal aging process will be easy to detect in the early stages. Three of the diseases that find extensive research are described below.

ALZEIMER:

In Alzheimer disease, there is a huge decrease in the total number of neurons (in [18] %40-50) and the cerebral cortex is significantly reduced in volume, with the greatest loss from the medial temporal structures [19]. Brain atrophy is the key symptom in AD, resulting from the neuronal and synaptic loss. Sitoh *et al.* [21] compares the cerebral and hippocampus volumetry in early Alzheimer's disease and found that AD group had smaller total cerebral and hippocampus volumes and total brain volume and hippocampus.

However, there have been conflicting results involving the clinical significance of white matter changes in patients with Alzheimer's disease (AD) in the terms of if the brain atrophy is caused by WM volume changes or not.

Salat *et al.* [20] compares the gray and white matter volumes in healthy aging and Alzheimer disease. Double *et al.* [19] compares the brain atrophy of the aged and diseased brains. Although the Alzheimer disease (AD) has symptoms like a fast aging process, these two studies show that Alzheimer disease is not the same thing as accelerated aging. The decrease in the white matter and gray matter was found to be similar in the old health elderly people and in the people with the AD. So it can be deducted from these results that the atrophy of brain in AD is not similar to aging, but it is a specific damage of AD.

MULTIPLE SCHLEROSIS:

Multiple sclerosis (MS) is a disease of the white matter in which the myelin sheaths of axons are damaged. MRI is a sensitive tool to monitor this disease and the MS lesions appear as the hyper intense regions in the brain in an MR image. While brain atrophy occurs early in the clinical course of multiple sclerosis, exactly how early, which tissues are affected and the rate at which early atrophy occurs are unclear.

IMPAIRED MOBILITY IN OLDER PERSONS:

The findings of [22] show that in elders with impaired mobility, increased white matter signal abnormalities are detected. The study reports that the decrease in white matter volume was observed which was age related, but the white matter signal abnormalities were not age related and they were found to be double of the control subjects. Thus the paper suggests that the increase in white matter signal abnormalities can be a factor of motor disability.

CONCLUSION:

These studies all try to serve one point: if it will be possible to define when and where the aging starts, if some protective factors can be developed to slow down the changes associated with aging, and if the patterns of diseases such as Alzheimer, schizophrenia, multiple sclerosis, schizophrenia, alcoholism and AIDS related dementia can be detected and separated from the changes occurring due to aging. These questions still remain a problem, and any information found from MR images will not give the sufficient answers. Extensive combined research on other areas will also be needed to come to such a conclusion.

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