Quantitative Metrics for White Matter Integrity Based on Diffusion Tensor MRI Data

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ABSTRACT

We present several new metrics of white matter integrity derived from multi-directional diffusion MRI measurements. The metrics are based on tracts of interest (TOIs) and measure properties of those tracts. TOIs are defined as a subset of representative streamtubes within a brain. For example, the whole brain is a TOI, as is a selection of streamtubes representing the cingulum bundle. In our work, these TOIs are selected interactively. For a given TOI, our metrics include the total length of all streamtubes, the weighted length of all streamtubes, and the number of streamtubes in the TOI. We demonstrate these metrics for 12 healthy volunteers, 6 subjects with vascular cognitive impairment (VCI), 1 human immunodeficiency virus (HIV) subject, and 1 HIV subject with Progressive Multifocal Leukoencephalopathy (PML), a disease that develops in the context of significant immunosuppression and is characterized by a high degree of white matter pathway deterioration. In addition, we demonstrate the reproducibility of these results by looking at the ability of the seeding and culling approach to streamtube generation, as proposed by Zhang et al. [8], to produce a representative set of streamtubes.

INTRODUCTION

Diffusion tensor imaging (DTI) is a type of magnetic resonance imaging (MRI) that measures the directionally dependent rate of self-diffusion of water at each sample point. These measures are in the form of a diffusion tensor, which can be decomposed into three nonnegative eigenvalues and three eigenvectors that describe how water diffuses at a given sample point [1]. Because of the high degree of organization of white matter in the brain, water diffusion in white matter will tend to be anisotropic. More specifically, water will tend to diffuse more rapidly in directions along white matter tracts because physical barriers such as axonal walls restrict water movement in other directions. Because DTI highlights areas of white matter, it provides a means of studying white matter structure in the brain. The importance of DTI is underscored by the fact that it is currently the only way of studying white matter structure *in vivo*. Being able to study white matter structure *in vivo* is key to being able to understand how these connections in the brain are affected during the progression of various diseases, and how cognitive and behavioral symptoms are tied to these changes.

Because of the complexity of DTI data, various methods of quantitative analysis, such as collapsing each tensor into a scalar index, have been proposed. For example, Basser et al. [2] proposed the use of the scalar indices of relative anisotropy (RA) as well as the widely used fractional anisotropy (FA). However, in converting a diffusion tensor to a scalar index, the information on the shape of water diffusion at the corresponding sample point is lost. Westin et al. [7] proposed measures of spherical, linear, and planar diffusion (c_s, c_l, c_p, respectively) to more completely represent the tensor.

Building off of Westin's metric of linear diffusion, we present three metrics that may be used to quantify the overall white matter health of whole tracts of interest (TOIs) within the brain. We first demonstrate the reproducibility of our measures on a given set of data. We then demonstrate the use of these metrics in applications to a group of healthy subjects, and we investigate these metrics in the context of the following pathologies: vascular cognitive impairment (VCI), human immunodeficiency virus (HIV), and HIV with progressive multifocal leukoencephalopathy (PML).

RELATED WORK

Because of the complex nature of diffusion tensor data, several visualization techniques have been proposed to present the data in a more understandable manner. For example, arrays of glyphs such as ellipsoids may be used to visualize DTI data with each glyph representing a tensor [2, 4, 6]. More relevant to our work is the technique of tractography. In particular, we build off of the seeding and culling approach to streamtube generation proposed by Zhang et al. [8]. The trajectory of each streamtube is based on the major eigenvectors of a diffusion tensor field. Streamtubes, therefore, represent possible locations and orientations of white matter tracts in the brain. Dense sets of streamtubes are generated from seed points in the data volume. These streamtubes are then culled in order to obtain a smaller, representative set. Sherbondy et al. [3] allow for interactive exploration of tractography results through a dynamic query approach where a user places box- or ellipsoid-shaped volumes of interest (VOIs) in order to define regions of interest (ROIs). Our approach also builds on this interactive work.

On a more quantitative level, several metrics for analysis of diffusion tensor data have been proposed. For example, fractional anisotropy (FA), proposed by Basser et al. [2], is a commonly used scalar index. Because metrics such as linear, planar, and spherical diffusion, as proposed by Westin et al. [7], more completely represent a given tensor, for this paper we have focused more on these measures. These measures are defined as follows:

$$c_l = (\lambda_1 - \lambda_2) / \lambda_1 \quad (1)$$

$$c_p = (\lambda_2 - \lambda_3) / \lambda_1 \quad (2)$$

$$c_s = \lambda_3 / \lambda_1 \quad (3)$$

where c_l, c_p, and c_s are the measures of linear, planar, and spherical diffusion, respectively, and where λ_1, λ_2, and λ_3 are the three real eigenvalues associated with a diffusion tensor, and $\lambda_1 \geq \lambda_2 \geq \lambda_3 \geq 0$.

While these measures are based on individual tensors, we aim to extend off of them in order to measure the overall white matter integrity within a TOI.

METHODS

TOI Selection

We interactively select TOIs using the VOI approach of Sherbondy et al. [3]. Users define box-shaped VOIs and boolean expressions in order to select the streamtubes of interest. After the selection of a TOI, the user may choose to threshold the selection according to a minimum linear anisotropy level. Therefore, after a threshold is set, any streamtubes that have average linear anisotropies below the threshold are removed from the TOI.

For each subject, we identified two TOIs: the whole brain, and streamtubes that pass through the corpus callosum. After selecting these TOIs, we computed our proposed metrics, discussed next, on these TOIs in their unthresholded state as well as at a threshold of $c_l = 0.25$ in order to focus more on areas that are more highly linearly anisotropic.

Proposed Metrics

We propose the use of three new metrics as potential measures of overall white matter health within a TOI. Letting S be the set of streamtubes within a given TOI, we define the total length TL of a TOI to be:

$$TL = \sum_{\forall s \in S} L_s \quad (4)$$

where L_s is the length of a streamtube s in S. Because many pathologies affect the white matter connectivity in the brain, we believe that the DTI data for a diseased brain may result in a streamtube model consisting of shorter streamtubes in the effected regions of the brain than

would the DTI data for a healthy brain. Therefore, we would expect that the total length of a TOI that includes a damaged area of the brain would be less than the total length of the corresponding TOI in a healthy brain.

Building off of total length, we define the weighted length *WL*, our second metric, as:

$$WL = \sum_{\forall s \in S} C_s \times L_s \tag{5}$$

where C_s is the average linear anisotropy within streamtube *s*. We weight the lengths of streamtubes because, when comparing two streamtubes of the same length, our total length measure would imply that the two streamtubes might be equally healthy. However, if the first streamtube has a higher average linear anisotropy than the second, the first streamtube may represent a part of a tract that has a higher degree of white matter integrity than the second. Therefore, we would expect that the more damaged the TOI, the lower the weighted length.

We also normalized total length and weighted length by approximate intracranial volume in order to compare across subjects. Our motivation in using both types of metrics is that normalizing the total and weighted lengths may provide a measure of the severity of white matter damage relative to the healthy brain, whereas total and weighted lengths that are not normalized may provide a measure of cognitive function. We approximate total intracranial volume by first defining a box enclosing the brain. We defined the height of the box as the number of axial T_2-weighted MRI slices that intersect the brain intracranial volume from the most superior point to the base of the cerebellum, the width of the box as the number of sagittal slices that intersect the brain, and the depth as the number of coronal slices that intersect the brain. We then approximated the intracranial volume with the volume of an ellipsoid circumscribed by the box. Note, however, that this method of approximating intracranial volume is dependent on the coordinate system in which the brain is scanned; rotations would result in slightly different approximation. In order to normalize TL and WL by approximate intracranial volume, we divided our length metrics by approximate intracranial volume over average intracranial volume. That is, we computed normalized total length (*NTL*) and normalized weighted length (*NWL*) as follows:

$$NTL = \frac{TL}{V / \overline{V}} \tag{6}$$

$$NWL = \frac{WL}{V / \overline{V}} \tag{7}$$

where *V* is approximate intracranial volume, and $\overline{V}$ is the average approximate intracranial volume among subjects.

As our third metric, we define the number of streamtubes *N* of the TOI to be:

$$N = |S| \tag{8}$$

In and of itself, the number of streamtubes in a TOI is not a useful measure because, depending on the nature of the white matter damage, a diseased brain may have more or fewer streamtubes than a healthy brain. For example, several small lesions may disrupt tracts at several points, leading to many short streamtubes rather than a few long streamtubes. In this case, a diseased brain may have more streamtubes than a healthy brain. However, if the diseased brain has axonal loss throughout the brain, the diseased brain may have fewer streamtubes than the healthy brain. We are interested in the number of streamtubes in a TOI because of its usefulness when considered with total and weighted lengths. For example, if a diseased brain has a total length that is less than that of a healthy brain, but the number of streamtubes in the diseased brain is larger than that of the healthy brain, then, on average, the diseased brain has shorter streamtubes than the healthy brain.

Reproducibility Study

Using the seeding and culling approach of Zhang et al. [8], we evaluated reproducibility by comparing streamtube models for one healthy subject created using three different sets of input parameters. For all models, the parameters were as follows: streamtube radius = 0.3mm, minimum average linear anisotropy along a tube = 0.1, maximum tube length = 10mm, minimum distance between tubes = 2 voxel dimensions, and step size = 1mm. The only variable parameter we used was the seeding parameter. If the seeding parameter is (x y z), then for every cube of size $(x \times v_x) \times (y \times v_y) \times (z \times v_z)$, where ($v_x$ v_y v_z) are the voxel dimensions, there is a seed point. For 8 of these models, we used a coarse seeding parameter of 2 2 2, for another set of 8 models, we used a seeding parameter of 1 1 1, and for the last set of 8 models, we used a finer seeding parameter of 0.75 0.75 0.75. We then computed the total number of streamtubes, total length, and weighted length for all models to see how consistent the models within each set were with each other and to see whether or not variability between models decreased with finer seeding.

Subjects

In order to demonstrate the potential of these metrics as measures of overall white matter integrity, we applied them to 12 healthy subjects (aged 49 to 83), 6 subjects with VCI (aged 45 to 75), 1 49-year old subject with HIV, and 1 42-year old subject with HIV and PML. We study VCI and HIV in particular because both VCI and HIV are common pathologies that are thought to affect white matter integrity.

RESULTS AND DISCUSSION

Reproducibility Study

Results

Table 1 shows the results of our reproducibility study. For the coarsest seeding parameter tested (2 2 2), the number of streamtubes, total and weighted lengths varied by about 0.75% around the mean in the unthresholded models. In the thresholded models, these metrics varied by about 1.67% around the mean. For a seeding parameter of 1 1 1, the number of streamtubes, total and weighted lengths varied around the mean by about 0.52% in the unthresholded models, and by about 1.39% in the thresholded case. For the finest seeding parameter tested (0.75 0.75 0.75), the metrics varied around the mean by about 0.43% in the unthresholded models, and by about 1.04% in the thresholded models.

Discussion

As these results show, when a coarser seeding parameter is used (for example, 2 2 2), there is a higher degree of variability between models generated with the same parameters than when a finer seeding parameter is used (for example, 0.75 0.75 0.75). In all three cases shown in Table 1, however, the variability is relatively small, as all three groups show variabilities of less than 2% above and below the average. For the data we present next, the models have been generated with a seeding parameter of 1 1 1.

Table 1 Results of the reproducibility study (mean ± SD)

	NO THRESHOLD			THRESHOLD = 0.25		
Seed	N	TL (mm)	WL (mm)	N	TL (mm)	WL (mm)
2 2 2	4243.38 ± 32.26	108909.77 ± 804.58	26957.10 ± 241.4	943.13 ± 14.22	45128.17 ± 902.15	14433.65 ± 267.41
1 1 1	5507 ± 21.01	138835.55 ± 797.99	33664.97 ± 238.4	1129.13 ± 10.66	54619.25 ±1018.38	17407.2 ± 284.86
0.75 0.75 0.75	5944.75 ± 27.15	150599.92 ± 652.69	36386.75 ± 145.64	1198.5 ± 16.17	58396.52 ± 537.56	18612.89 ± 158.9

Table 2 Whole Brain, Unthresholded Results (Mean ± SD (correlation with age r, p))

	N	TL (mm)	NTL (mm)	WL (mm)	NWL (mm)
12 Healthy Controls	5032.08 ± 692.82 (r = -0.53, p = 0)	119540.99 ± 21406.78 (r = -0.55, p = 0)	120190.32 ± 22656.39 (r = -0.84, p = 0)	29332.58 ± 5875.54 (r = -0.49, p = 0)	29467.70 ± 6004.99 (r = -0.78, p = 0)
6 VCI Subjects	4520 ± 1053.13 (r = -0.42, p = 0)	90703.59 ± 16988.76 (r = -0.46, p = 0)	92607.17 ± 23976.99 (r = -0.2, p = 0)	19920.81 ± 3269.85 (r = 0.02, p = 0)	20387.23 ± 5287.95 (r = 0.13, p = 0)
1 HIV Subject	5290	118605.73	118605.73	28804	28804.00
1 HIV/PML Subject	4250	84836.96	84836.96	19686.67	19686.67

TOI 1: Whole Brain

Unthresholded Results

Figure 1 (see Appendix of Figures) shows the sagittal views of unthresholded, whole brain streamtube models for 1 healthy control, 1 VCI subject, the HIV subject and the HIV/PML subject. Figures 2 and 3 show the unthresholded total and weighted lengths, respectively, of all subjects as a function of age. As Table 2 shows, there is a large correlation between age and number of streamtubes (r = -0.57), age and total length (r = -0.55), and age and weighted length (r = -0.49) among the healthy subjects. This does not appear to be true for the VCI subjects, especially in the case of the weighted lengths (r = 0.02).

The average number of streamtubes for the healthy subjects (N = 5,032) is greater than the average number of streamtubes for the VCI subjects (N = 4,520) and the HIV/PML subject (N = 4,250), but it is less than that of the HIV subject (N = 5,290). The average total length of the healthy subjects (TL = 119,540.99mm) and the average weighted length (WL = 29,332.58mm) are both greater than the corresponding values in the VCI and HIV groups.

Figures 4 and 5 show the unthresholded, normalized total and weighted lengths, respectively, of all subjects as a function of age. After normalizing these values, age and normalized total length (r = -0.84), and age and normalized weighted length (r = -0.78) in the healthy subjects still seem to show significant correlations. As in the previous case, there does not seem to be a significant correlation between age and normalized total length or between age and normalized weighted length in the VCI subjects. Normalizing also retains the relationships between the different subject groups, as the healthy group of subjects still has an average normalized total length (NTL = 120190.32mm) and an average normalized weighted length (NWL = 29467.70mm) greater than the VCI and HIV subjects.

Thresholded (minimum c_l = 0.25) Results

Figure 6 shows the sagittal views of the thresholded, whole brain streamtube models of 1 healthy subject, 1 VCI subject, 1 HIV subject, and 1 HIV/PML subject. Figures 7 – 10 show the total, weighted, normalized total, and normalized weighted lengths, respectively, of all subjects as a function of age. As shown in Table 3 shows, there is still a significant correlation between age and each of our metrics among the healthy subjects. The healthy group of subjects also has the greater values for all metrics when compared to the VCI and HIV groups.

Table 3 Whole Brain, Thresholded ($c_l = 0.25$) Results (Mean ± SD (correlation with age r, p))

	N	TL (mm)	NTL (mm)	WL (mm)	NWL (mm)
12 Healthy Controls	1093.42 ± 263.91 (r = -0.31, p = 0)	49,624.86 ± 13924.08 (r = -0.39, p = 0)	49738.59 ± 13523.55 (r = -0.62, p = 0)	15800.42 ± 4299.96 (r = -0.37, p = 0)	15835.18 ± 4171.66 (r = -0.60, p = 0)
6 VCI Subjects	795.83 ± 475.13 (r = -0.17, p = 0.01)	28730.46 ± 5618.40 (r = -0.23, p = 0)	29418.28 ± 7968.42 (r = -0.04, p = 0)	9200.84 ± 1748.23 (r = -0.18, p = 0)	9421.06 ± 2521.83 (r = 0, p = 0)
1 HIV Subject	1011	46553.09	46553.09	14807.89	14807.89
1 HIV/PML Subject	804	29679.32	29679.32	9089.62	9089.62

Discussion

Figures 1 – 10 show that the VCI subjects generally have lower total and weighted lengths in the unthresholded case. While both the healthy subjects and the VCI subjects show high variabilities, performing a T-test reveals that, with the exception of the number of streamtubes, the differences between the healthy subjects and the VCI subjects according to our metrics are statistically significant. Since the difference in the number of streamtubes between the healthy controls and the VCI subjects does not appear to be significant while the measures of total length and weighted length is significantly smaller in the VCI subjects, it is implied that the VCI subjects have, on average, shorter and less linearly anisotropic streamtubes than the healthy controls. In order to determine whether the white matter damage in the VCI subjects affects all regions of the brain or certain regions in particular, it would be necessary to compute these metrics on smaller TOIs. We consider streamtubes running through the corpus callosum in the following section.

The HIV subject has total and weighted lengths within the range of mean ± SD for the healthy subjects. The HIV subject with PML, on the other hand, has total and weighted lengths that are both far less than those of the healthy subjects. It is of note that this particular HIV patient had a CD4 cell count greater than 800 and a very low viral load. The observation that his total and weighted lengths were within the range of the healthy controls is consistent with previous studies demonstrating limited, if any, brain dysfunction among HIV patients with good immunological status [5]. By contrast, the addition of PML in the context of HIV was characterized by a marked decrease in white matter integrity overall.

When these measures of total and weighted lengths are normalized by approximate intracranial volume, there seems to be a stronger relationship between age and total length, and between age and weighted length. However, the relationships between the group of healthy subjects and the VCI, HIV, and HIV/PML groups remain the same. That is, the VCI group generally has lower normalized total and weighted lengths than the healthy group. The normalized total and weighted lengths for the HIV subject, again, fell well within the range of mean ± SD for the healthy subjects, while the HIV subject with PML fell well below this range.

For a TOI of the whole brain thresholded at a linear anisotropy level of 0.25, the story is slightly different. While the difference in the number of streamtubes between the healthy controls and the VCI subjects, again, does not seem significant, the differences between these groups in total and weighted lengths, and normalized total and weighted lengths are more significant in this thresholded case than in the unthresholded case.

As in the unthresholded case, the total and weighted lengths for the HIV subject are smaller than for the healthy subjects, although they are still within the range of the healthy mean ± SD. The HIV subject with PML, on the other hand, fell well below this range, indicating that the severity of white matter damage is greater in the HIV subject with PML than in the HIV subject without PML. As in the unthresholded case, the normalization of the metrics makes the relationship of these metrics with age more apparent.

While these metrics appear to be highly correlated with age in the healthy subjects, our data does not imply a similar high correlation in the VCI subjects. A possible explanation for this is that the effects of VCI change this age correlation.

TOI 2: Corpus Callosum

Unthresholded Results

As our second TOI, we investigated our metrics in fibers going through the corpus callosum. Figure 11 shows the unthresholded, sagittal view of the TOI selection in one of the healthy subjects, one VCI subject, the HIV subject and the HIV subject with PML. Table 4 shows the means and standard deviations of our metrics within the different groups of subjects while Figures 12 – 15 show the specifics of each group of subjects in the unthresholded case. In the unthresholded corpus callosums of the normal controls, there does not seem to be a significant correlation between age and total length, or age and weighted length, unlike the case of the whole brain TOI. Here, the correlation coefficient of age and total length is $r = –0.06$, and the correlation coefficient of age and weighted length is $r = –0.01$ for the healthy subjects. There also does not appear to be a correlation between our metrics and age among the VCI subjects, as was the case in the whole brain TOI.

The average number of streamtubes, the average total lengths, and the average weighted lengths for the VCI subjects were lower than the averages of the healthy subjects (N = 236.5, TL = 14265.26mm, WL = 4979.87mm), the HIV/PML subject had the lowest measures, while the HIV subject (N = 268, TL = 15570.8mm, WL = 5355.54mm) had measures greater than the averages of the healthy controls. The same relationships hold for the normalized measures.

Table 5 Unthresholded, corpus callosum results (mean ± SD (age correlation r, p))

	N	TL (mm)	NTL (mm)	WL (mm)	NWL (mm)
12 Healthy Controls	236.5 ± 35.08 (r = -0.06, p = 0)	14265.26 ± 4831.84 (r = -0.07, p = 0)	14337.15 ± 4832.76 (r = -0.23, p = 0)	4979.87 ± 1743.30 (r = -0.01, p = 0)	4999.76 ± 1728.11 (r = -0.17, p = 0)
6 VCI Subjects	214 ± 52.68 (r = -0.19, p = 0)	9276.21 ± 3583.71 (r = 0.05, p = 0)	9714.53 ± 4649.70 (r = 0.09, p = 0)	3075.33 ± 1312.57 (r = 0.10, p = 0)	3232.23 ± 1659.49 (r = 0.13, p = 0)
1 HIV Subject	268	15570.80	15570.8	5355.54	5355.54
1 HIV/PML Subject	125	3856.92	3856.92	1164.96	1164.96

Table 4 Thresholded (cl = 0.25), corpus callosum results (mean ± SD (age correlation r, p))

	N	TL (mm)	NTL (mm)	WL (mm)	NWL (mm)
12 Healthy Controls	172.92 ± 41.14 (r = -0.02, p = 0)	12318.39 ± 4970.44 (r = -0.01, p = 0)	12357.78 ± 4887.68 (r = -0.15, p = 0)	4568.03 ± 1766.22 (r = 0.03, p = 0)	4580.36 ± 1733.29 (r = -0.11, p = 0)
6 VCI Subjects	142.67 ± 65.25 (r = -0.1, p = 0.01)	7135.98 ± 3233.54 (r = 0.08, p = 0)	7507.49 ± 3950.56 (r = 0.12, p = 0)	2630.55 ± 1243.85 (r = 0.12, p = 0)	2772.39 ± 1512.88 (r = 0.15, p = 0)
1 HIV Subject	199	13472.7	13472.7	4886.85	4886.85
1 HIV/PML Subject	74	2795.06	2795.06	941.94	941.94

Thresholded (minimum $c_l = 0.25$) Results

Table 5 shows the means and standard deviations of our metrics within the different groups at a threshold of $c_l = 0.25$. Figures 16 – 19 show the thresholded total length, weighted length, normalized total length, and normalized weighted length results, respectively. Again, there does not seem to be a correlation between our metrics and age in the healthy group of subjects. As was the case in the unthresholded TOI, the measures for the HIV subject with PML ($N = 74$, $TL = 2795.06$mm, $WL = 941.94$mm) are much lower than the averages of the healthy subjects ($N = 172.92$, $TL = 12318.39$mm, $WL = 4568.03$mm), the VCI subjects ($N = 142.67$, $TL = 7135.98$mm, $WL = 2630.55$mm), and the HIV subject ($N = 199$, $TL = 13472.7$mm, $WL = 4886.85$mm). The same is true for the normalized measures.

Discussion

Unlike the whole brain case where there seems to exist a high correlation between age and our metrics in healthy subjects, there seems to be no significant correlation in the case of the corpus callosum. This implies that while the brain as a whole declines as age increases, the corpus callosum may undergo smaller changes.

In the unthresholded case, the differences in total and weighted lengths between the healthy controls and the VCI subjects appear to be significant (t-tests resulted in a probability of $p = 0.03$ for total length, and $p = 0.02$ for weighted length), whereas the differences in normalized total and weighted lengths may not be significant. In the thresholded case, with the exception of the number of streamtubes, the differences between the healthy subjects and the VCI subjects appear to be significant. It is, therefore, suggested that the VCI subjects have some degree of overall white matter damage in the corpus callosum when compared to healthy controls.

The HIV subject, on the other hand, does not seem to have significant damage to the corpus callosum, as our measures for this subject are greater than the averages among the healthy controls. Qualitatively, this also appears to be true when considering Figure 11, since the TOI selected in the HIV subject appears no different from the healthy subject. However, based on both the quantitative and qualitative data, the HIV subject with PML appears to have a high degree of white matter damage in this TOI. This particular patient exhibited marked impairment across multiple cognitive domains, with pronounced deficits in the areas of executive function. These cognitive difficulties were evident behaviorally, as this patient became lost on three successive attempts to drive independently to the hospital for his cognitive evaluation. The nature of the cognitive deficits is also consistent with the anatomical location of his white matter damage, with pronounced changes evident in the frontal lobes.

Overall Discussion

In general, our results imply a significant difference in white matter integrity between the healthy controls, the VCI subjects and the HIV subject with PML. The HIV subject with PML, in particular, appears to have the greatest degree of white matter damage overall and when considering the corpus callosum in isolation. However, the white matter health of the HIV subject without PML, according to our metrics, may not be significantly different from the white matter health of our control group.

Our study of the whole brain as well as the corpus callosum suggests that, while there appears to be a significant correlation between age and overall white matter health in the entire brain for healthy subjects, it appears that some of the major white matter tracts, such as the corpus callosum, undergo minimal damage during aging. This seems to emphasize the importance of the corpus callosum as an important white matter tract in the brain.

Although our results are encouraging, there are a few points to consider. In terms of the methods used in this study, as this was a pilot study, total intracranial volume was approximated rather than measured. In the future, it would be necessary to use actual intracranial volumes when normalizing our metrics in order to see the actual effects of normalization on these metrics. Additionally, in future work, larger sample sizes and a smoother age distribution among subjects would give a better picture of the correlation between these metrics and age. Also, a trend does not seem to be apparent in the plots for the VCI subjects. A possible explanation for this is that the effects of VCI change the age-metric correlation that normally occurs in healthy patients.

With respect to TOI selection, in the future, it would be more ideal to automatically cluster streamtubes into tracts in order to minimize user interaction. A minimal amount of user interaction in TOI selection would increase consistency of TOI selection between subjects.

In terms of the metrics themselves, an important point to consider is that, because our metrics depend on the properties of TOIs, any motion during scanning would have an impact on the streamtubes generated and, in turn, would affect the calculations obtained from our metrics. In order to correct for this error, it may be possible to quantify the amount of motion during scanning and take this into account when calculating the number of streamtubes, total length and weighted length.

CONCLUSION

We have presented three new metrics for measuring white matter integrity in a given TOI. These metrics are based on the properties of the TOI under investigation. We have demonstrated the reproducibility of these measures as well as the potential of these metrics by applying the measures to a group of healthy subjects as well as groups of subjects with various pathologies. Our results show a significant, negative correlation between age and total/weighted lengths on the level of the whole brain in healthy subjects. In addition, according to our results VCI subjects and the HIV/PML subject generally have lower total and weighted lengths than normals, while the HIV subject remained within the (mean ± SD) range of the healthy subjects.

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APPENDIX: FIGURES

Figure 1 Unthresholded, whole brain streamtube models of a) a 61-year-old healthy volunteer b) a 59-year-old VCI subject c) the HIV subject and d) the HIV/PML subject

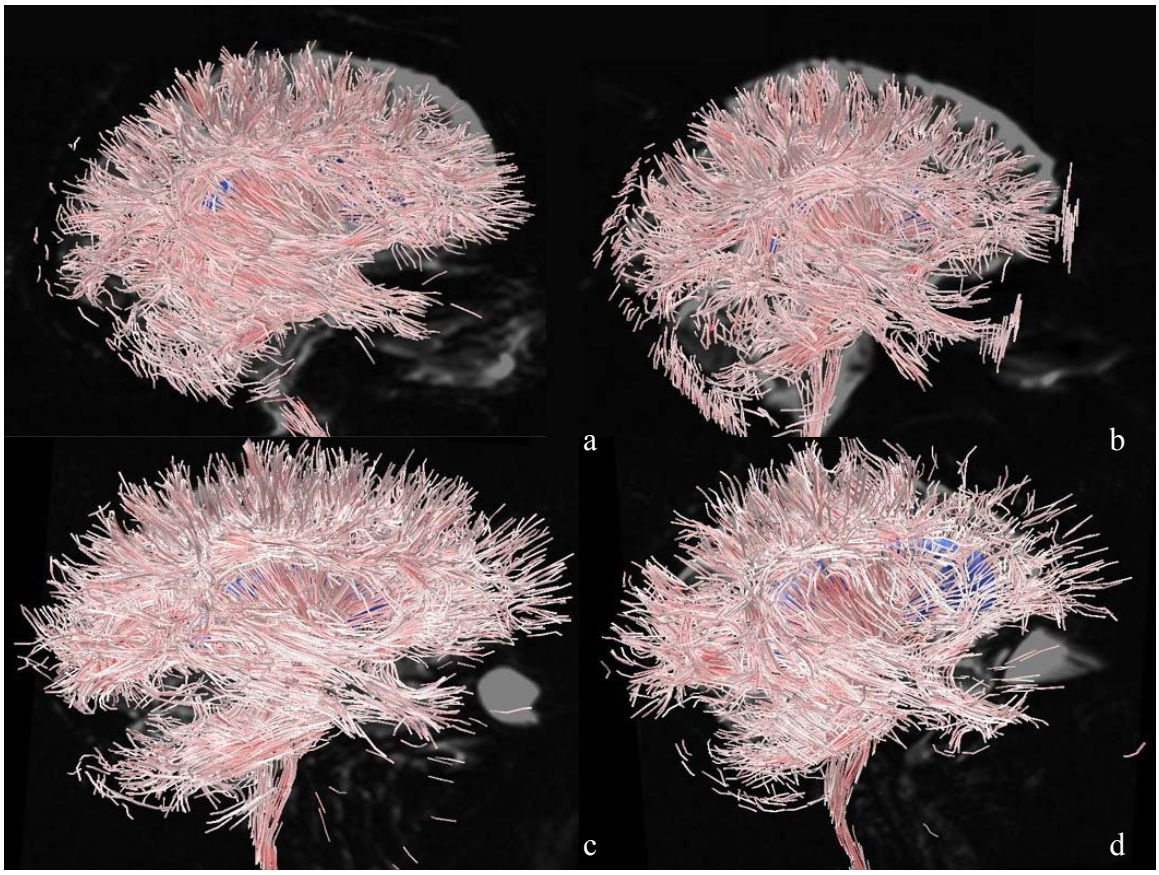

Figure 2 Unthresholded, whole brain total lengths

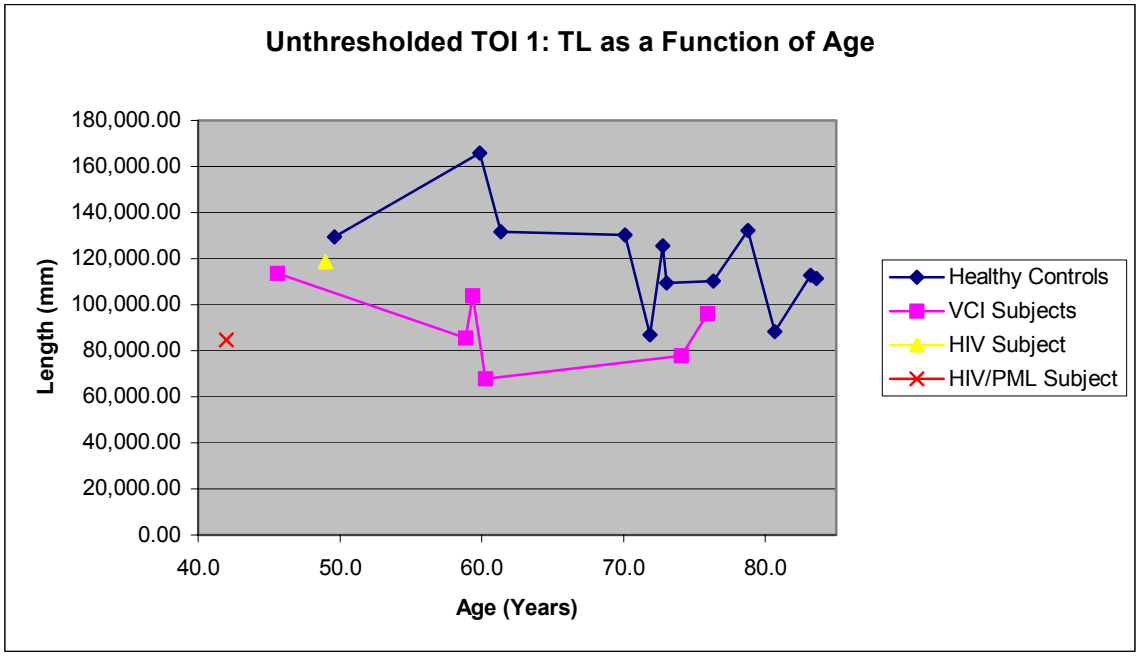

Figure 3 Unthresholded, whole brain weighted lengths

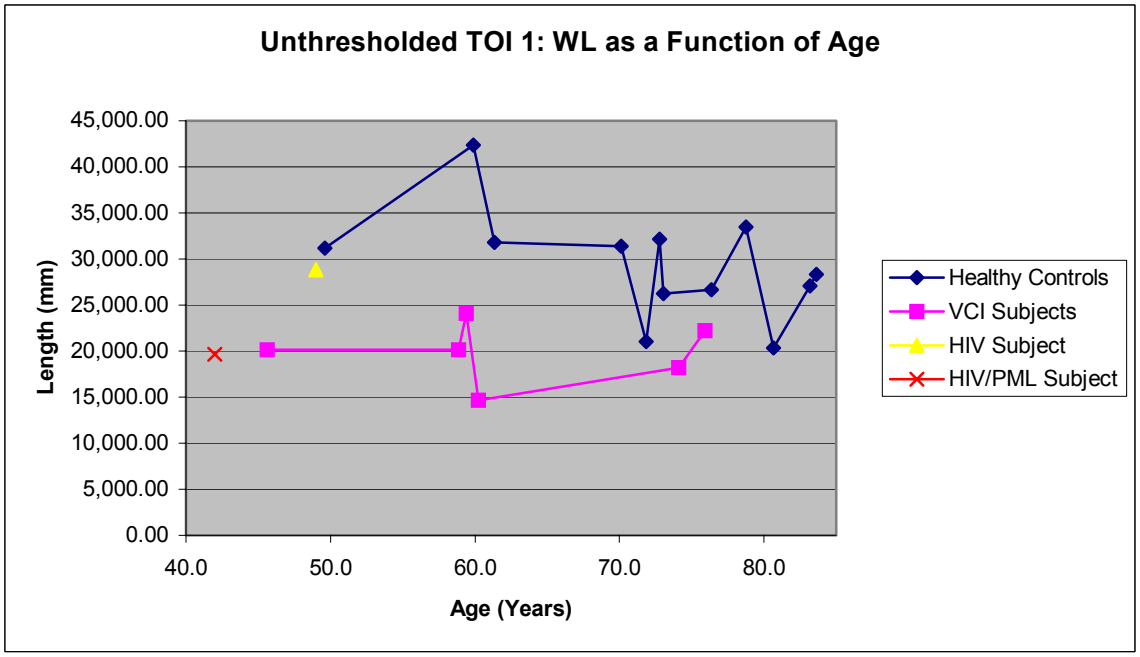

Figure 4 Unthresholded, whole brain normalized total lengths

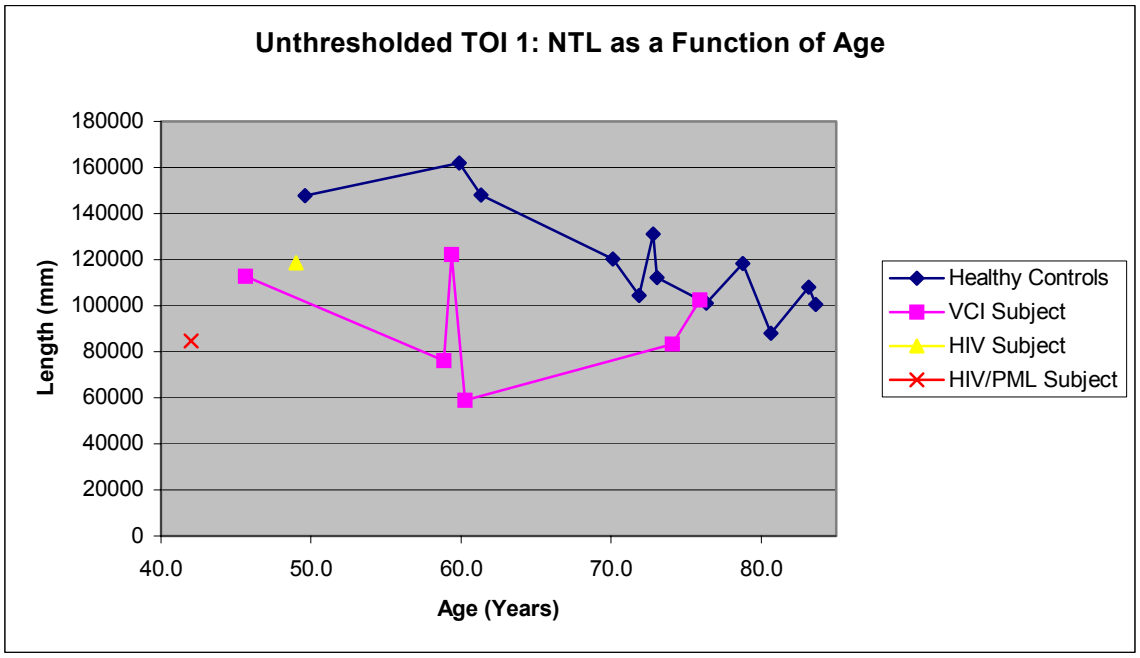

Figure 5 Unthresholded, whole brain NWL results

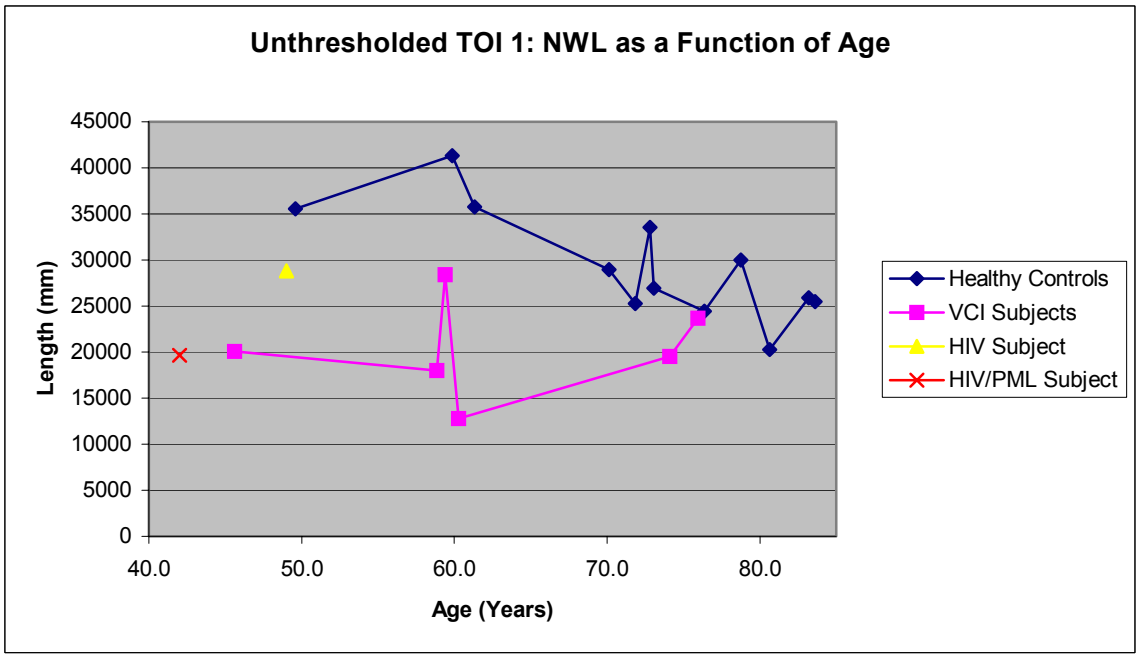

Figure 6 Thresholded, whole brain streamtube models of a) a 61-year-old healthy volunteer b) a 59-year-old VCI subject c) the HIV subject and d) the HIV/PML subject

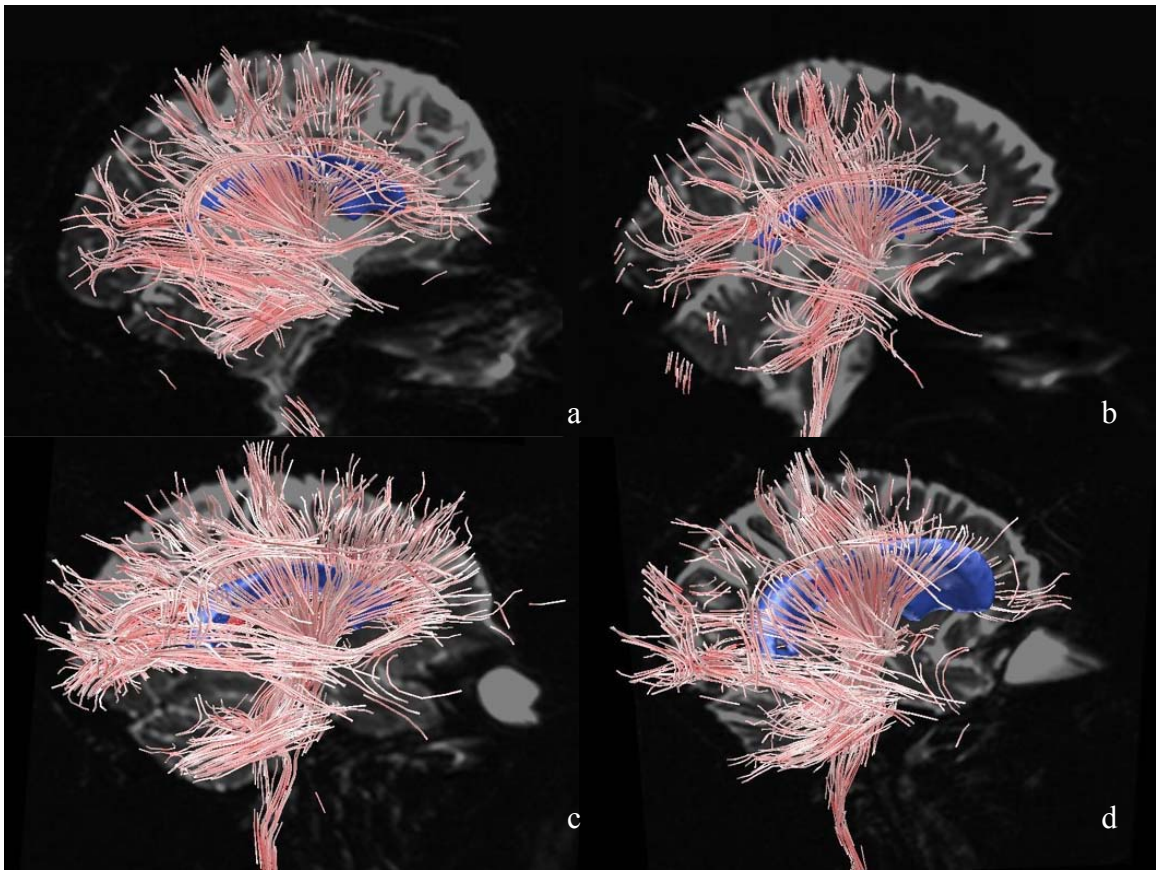

Figure 7 Thresholded, whole brain total lengths

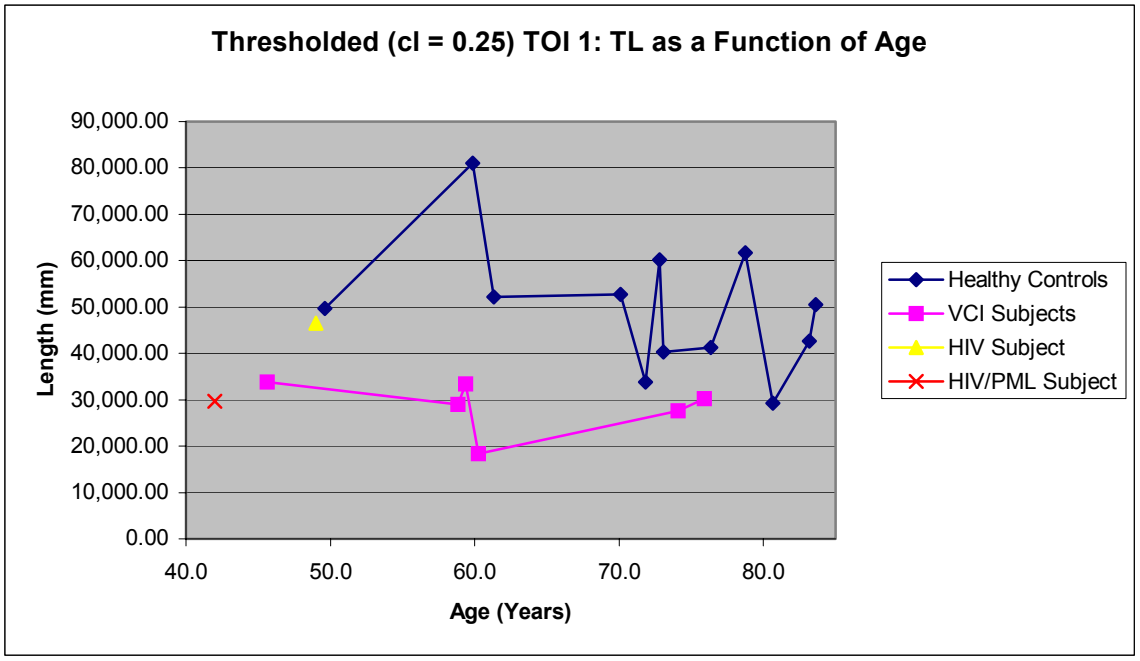

Figure 8 Thresholded, whole brain weighted lengths

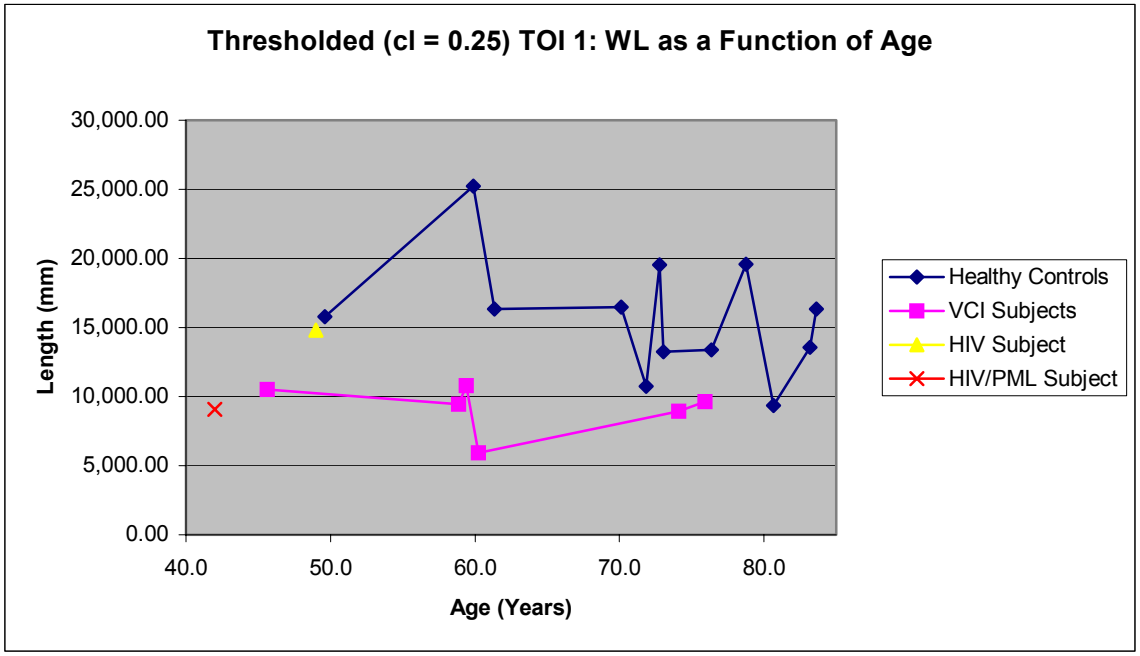

Figure 9 Thresholded, whole brain normalized total lengths

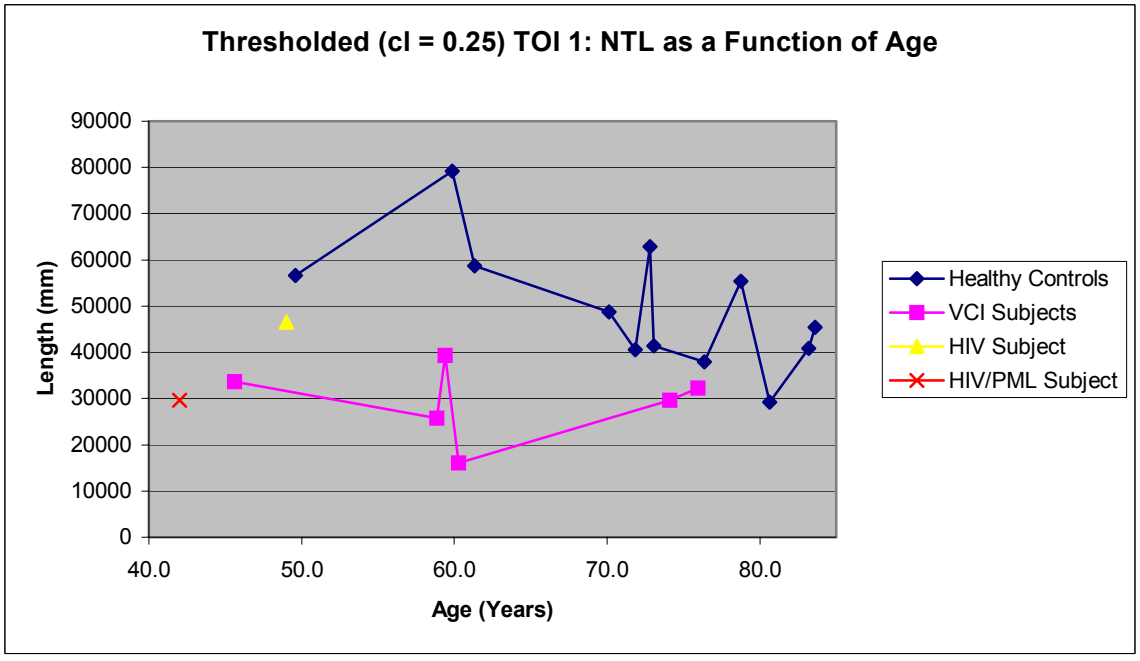

Figure 10 Thresholded, whole brain normalized weighted lengths

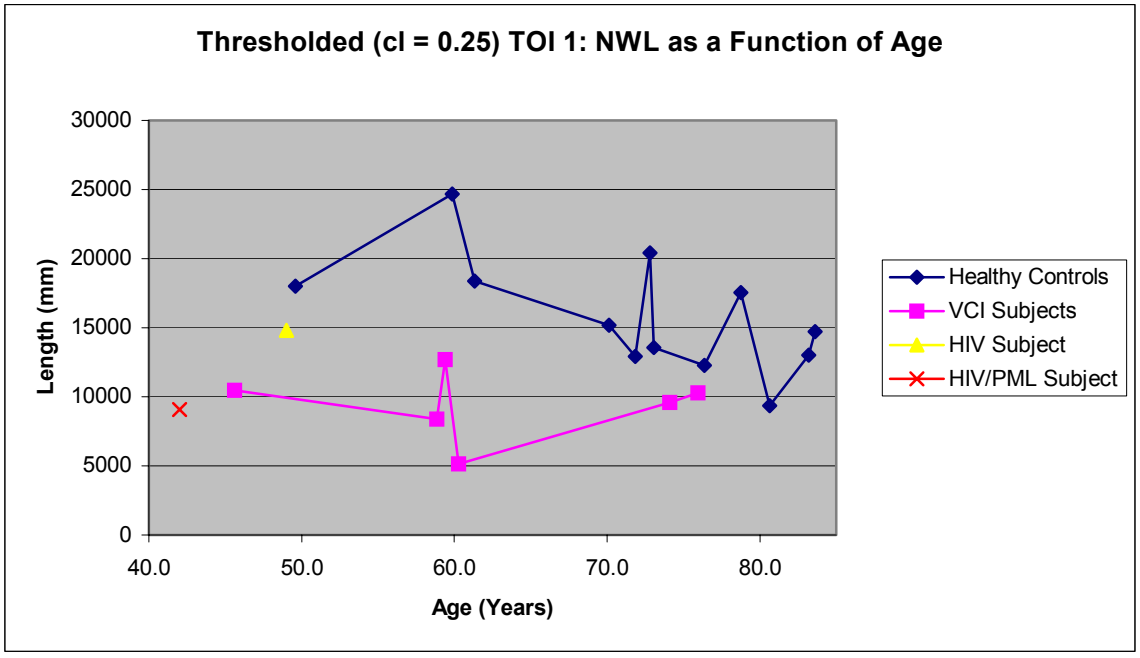

Figure 11 Corpus Callosum TOIs in (a) a 61-year-old healthy subject (b) a 45.6-year-old VCI subject (c) the HIV subject and (d) the HIV subject with PML

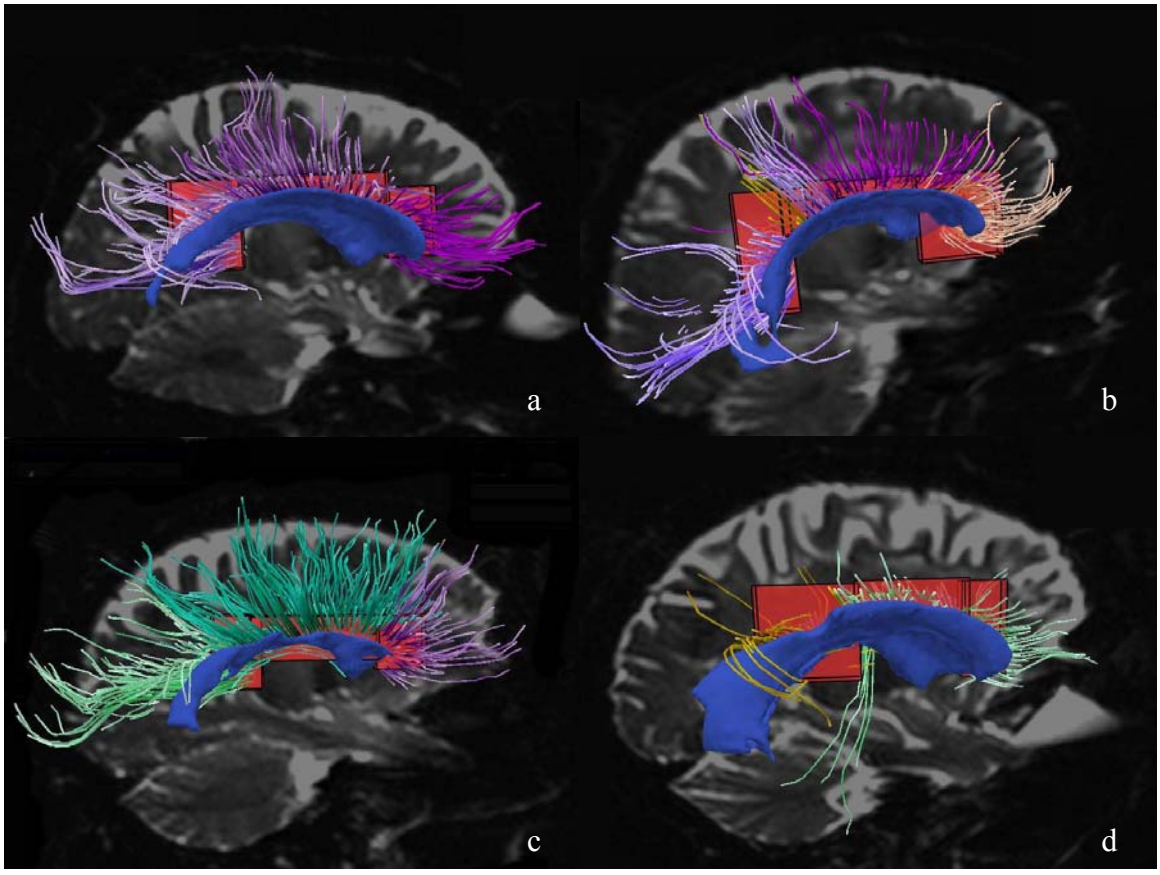

Figure 12 Unthresholded corpus callosum total lengths

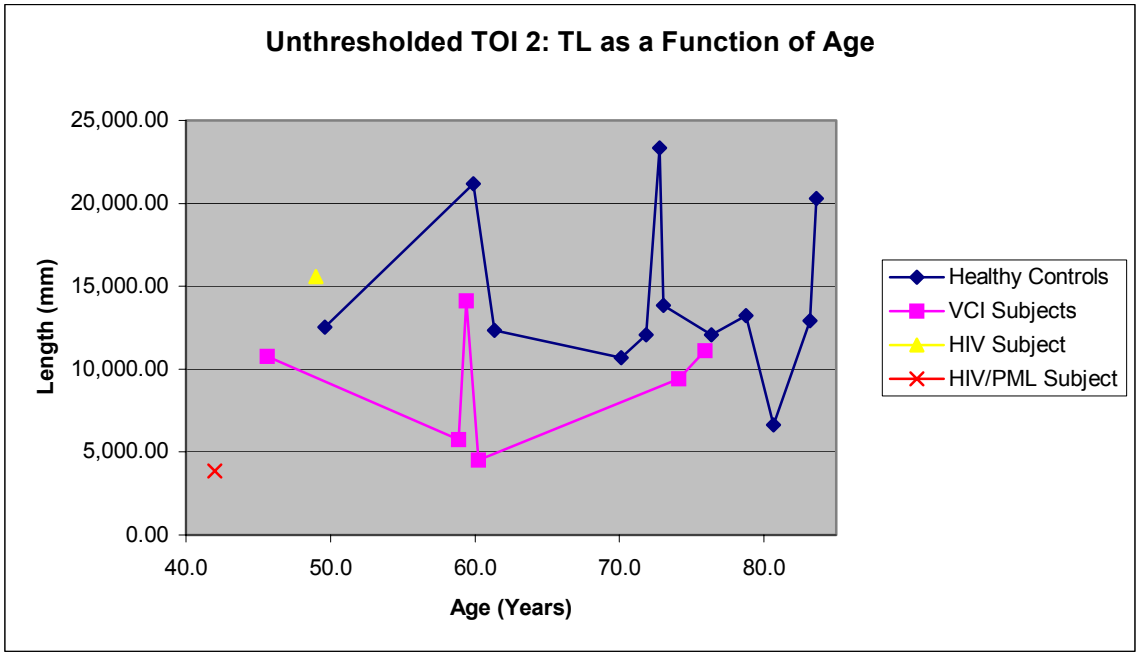

Figure 13 Unthresholded corpus callosum weighted lengths

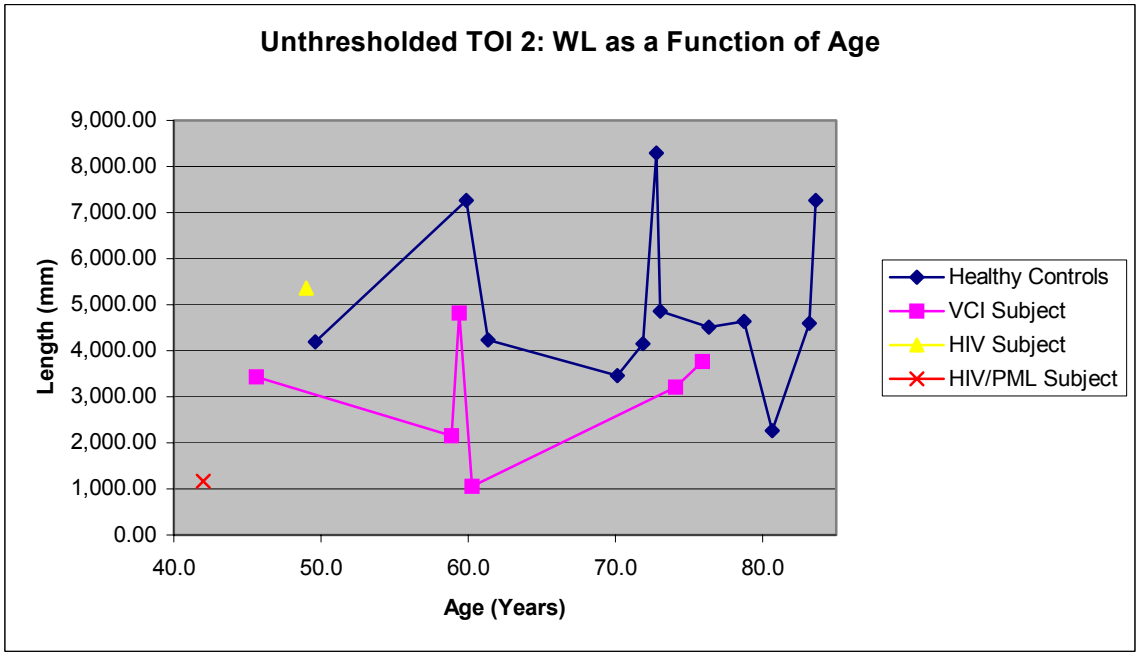

Figure 14 Unthresholded corpus callosum normalized total lengths

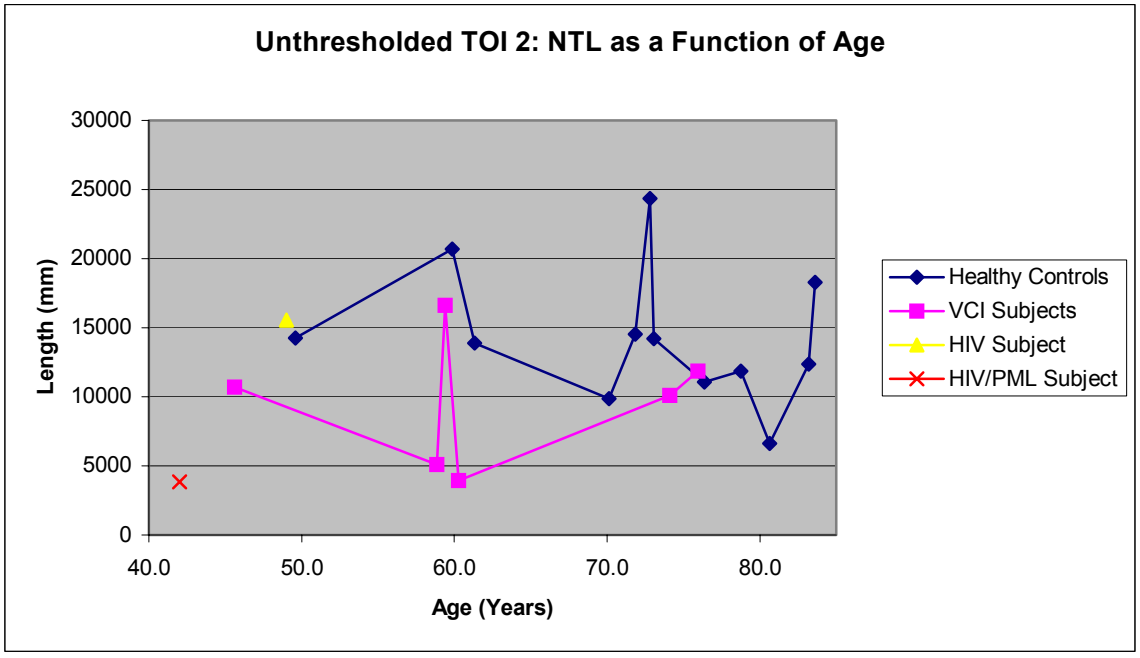

Figure 15 Unthresholded corpus callosum normalized weighted lengths

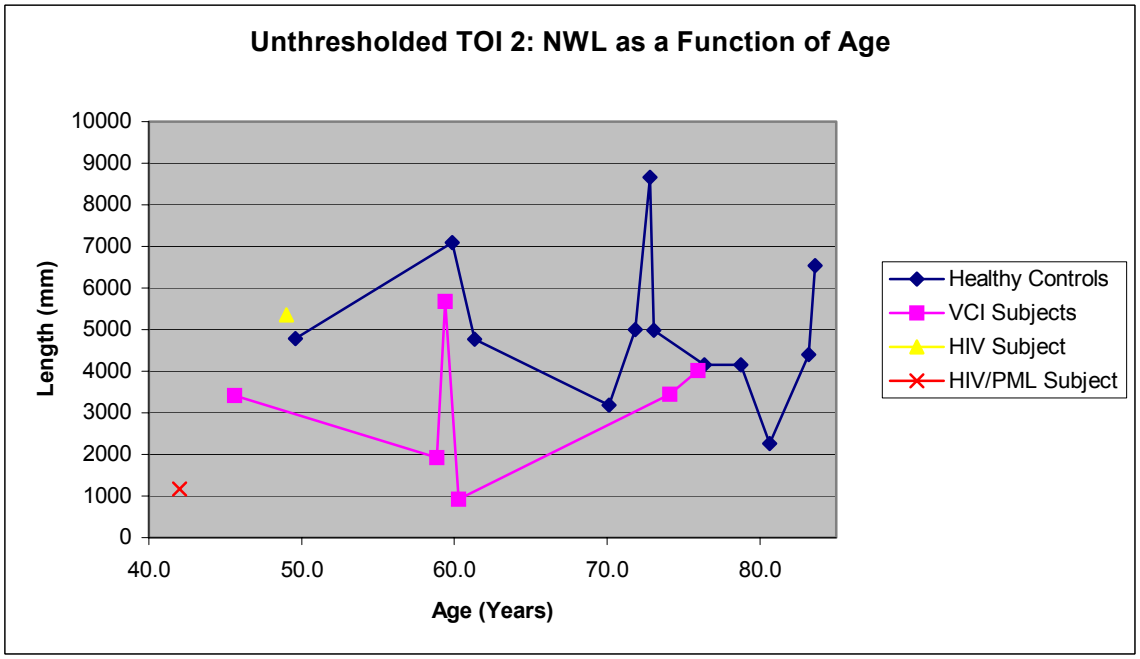

Figure 16 Thresholded corpus callosum total lengths

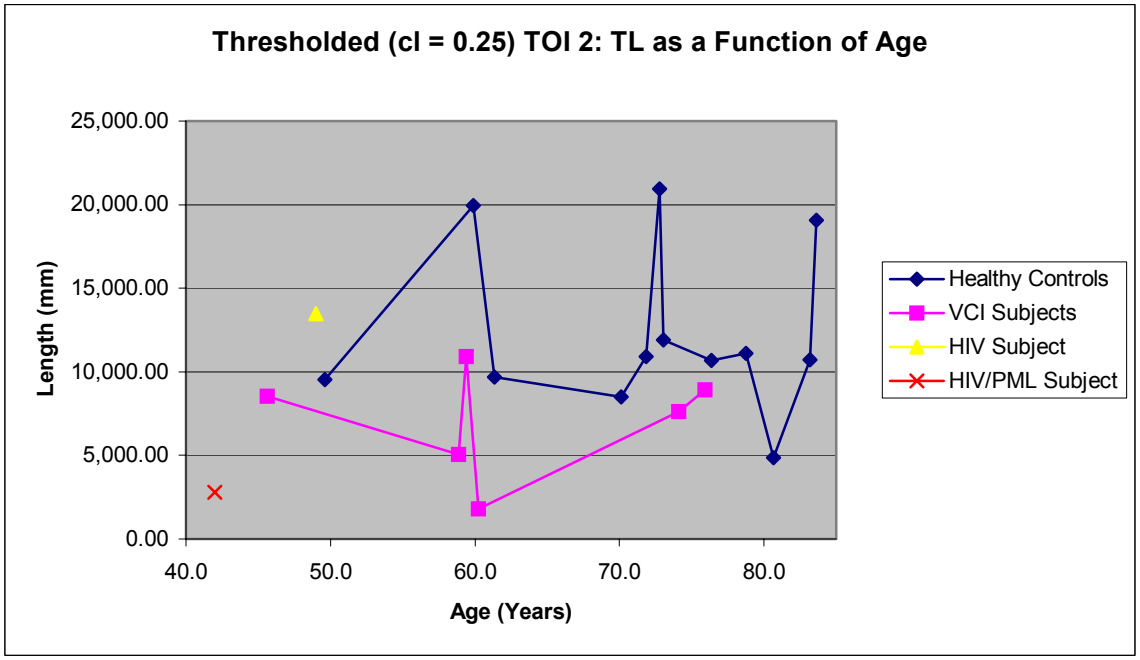

Figure 17 Thresholded corpus callosum weighted lengths

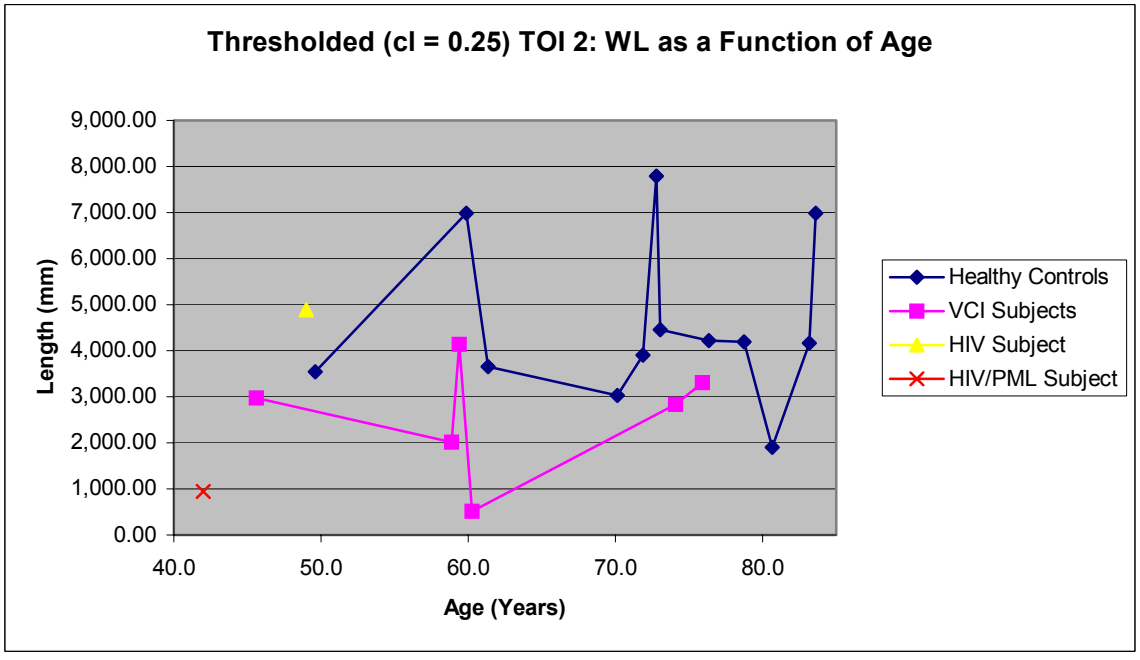

Figure 18 Thresholded corpus callosum normalized total lengths

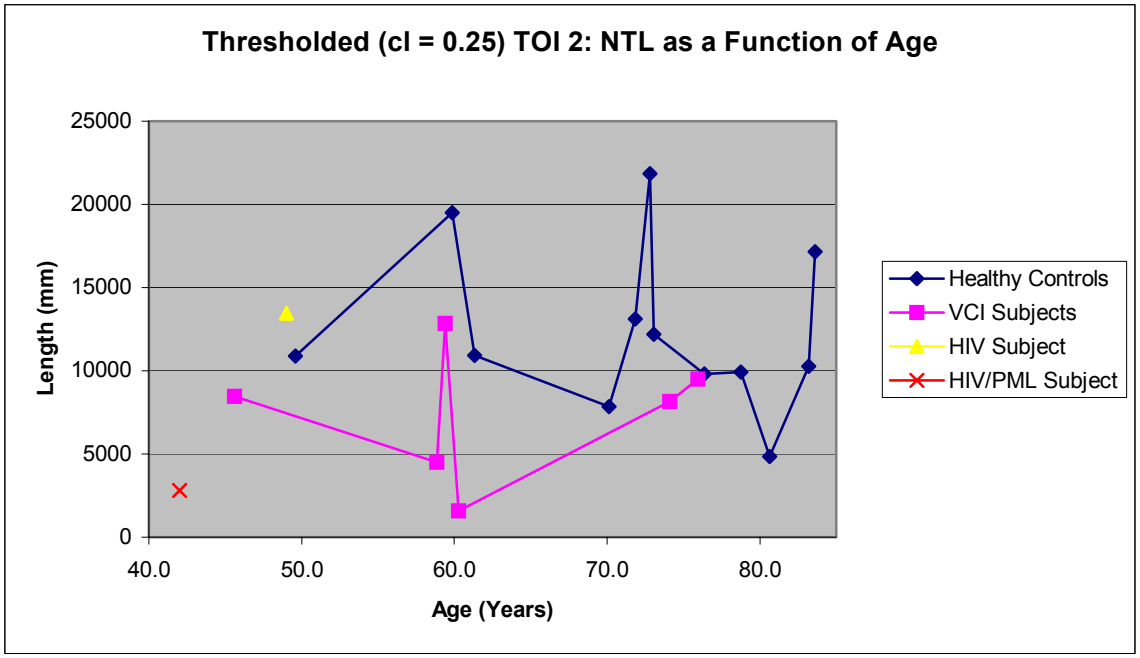

Figure 19 Thresholded corpus callosum normalized weighted lengths