An Analysis of LDDMM Distances for Morphometric Differences in Dendritic Spines of Mice due to Fragile X Syndrome

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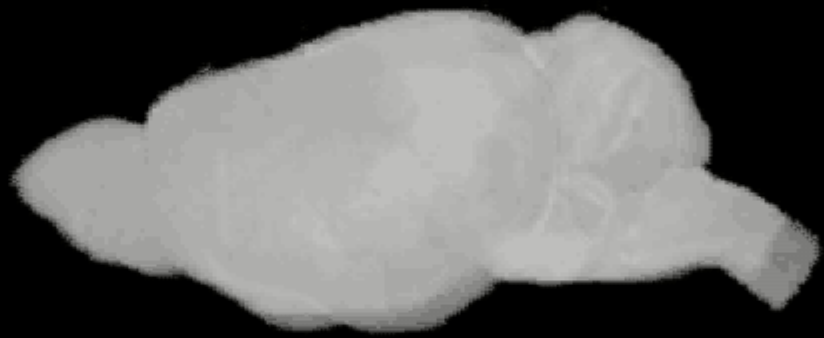


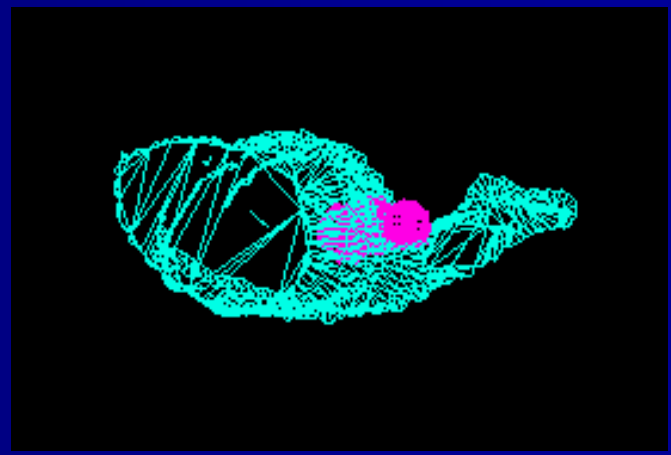
Introduction

The Large Deformation Diffeomorphic Metric Mapping (LDDMM) is a recently developed tool that quantizes morphometric (shape and size) differences between two images.

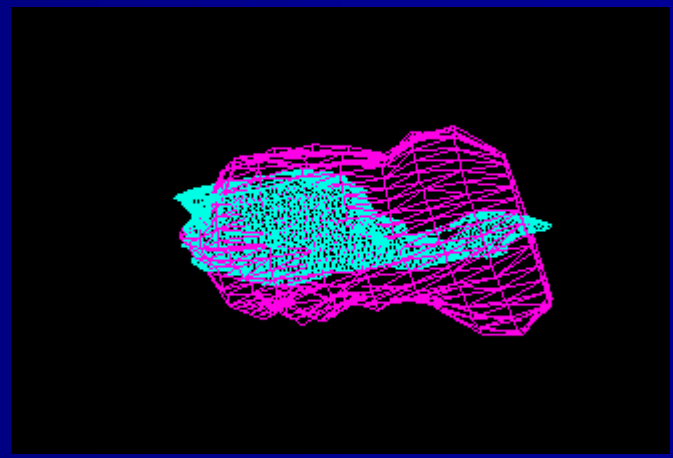
Our goal is to detect differences in LDDMM distances of dendritic spines due to the condition of mice: wild-type (control) or knock-out (fragile X syndrome).

Project Overview

1. Unscaled Data



2. Scaled Data



Unscaled Data Outline

1. We first run statistical analysis on LDDMM distances and condition only.

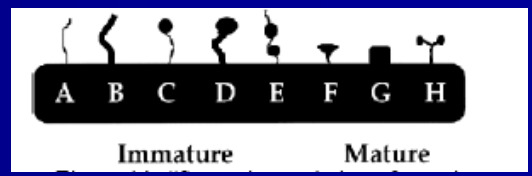
2. The dendritic spines are not matched for size and type of spine, so such factors might cause the group differences in the LDDMM distances, rather than the condition. Thus we include other variables into our analysis.

3. We run a linear model with LDDMM distances as the response variable and condition, type, volume, surface area, and height as predictor variables.

4. The influence of the condition on the LDDMM distances is analyzed after the influence of the type of spine, volume, surface area, and height is accounted for.

Description of Data

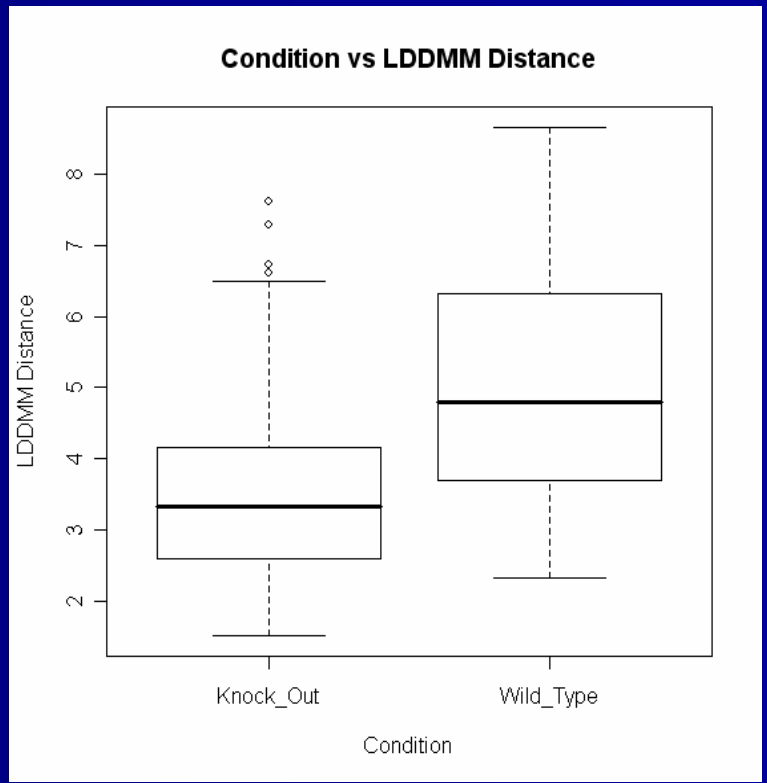
1. Condition of Mice
   The condition refers to whether the spine originated from a wild-type mouse or a knock-out mouse. The wild-type mice are expected to have a normal genetic make-up because they originate from natural mice populations. However, in the knock-out mice, the *Fmr1* gene is inactivated in order to mimic a human condition called fragile X syndrome. Fragile X syndrome is the most common form of inherited mental retardation in humans.
2. Type of Spine
   The type refers to the shape of the dendritic spine. The six types are double, flipodia, long mushroom, mushroom, stubby and thin.
3. Volume
4. Surface Area
5. Height
   For the height, 14 landmarks were placed on the surface of each dendritic spine, including one landmark for the neck, the point closest to the dendrite shaft, and one landmark for the head, the point furthest from the dendrite shaft. These landmarks were recorded into 3-D (x, y, z) coordinates. The height is the Euclidean distance between the neck coordinates and the head coordinates.



LDDMM Distances and Condition of Mice

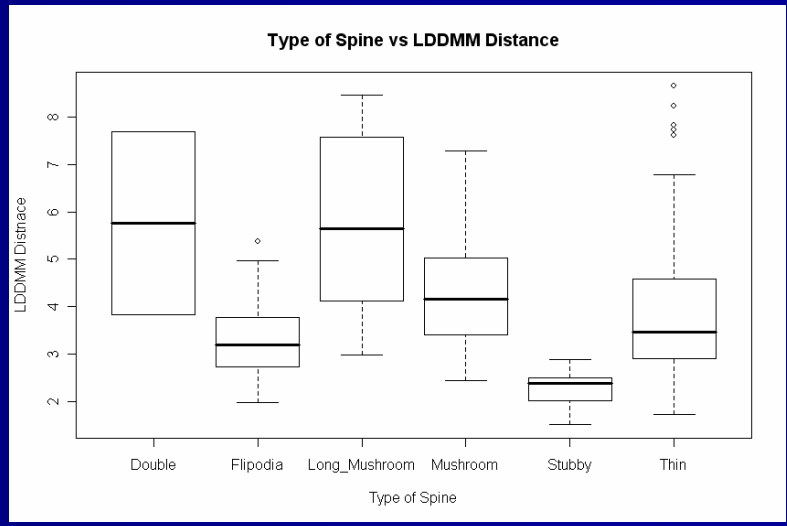
We perform a two-sample *t* test to determine if there is a significant difference in the LDDMM distance between the two conditions. The resulting p-value is 8.44×10^{-10}. This indicates that there is indeed a significant difference in the LDDMM distances between the wild-type mice and the knock-out mice.

However, the significant difference may be due to other factors, rather than the condition. Hence, we add the other factors to the set of predictor variables and then analyze the influence of the condition.



Analysis of Individual Variables: Type of Spine

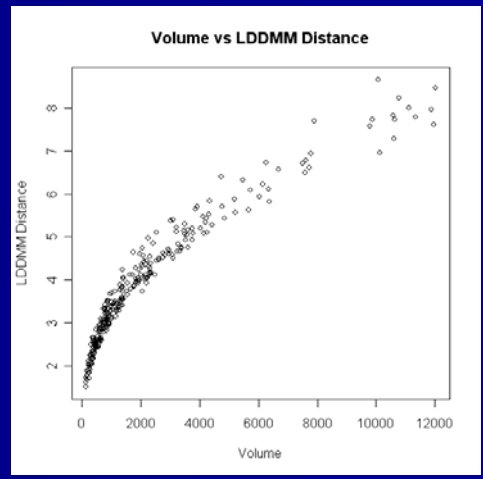
An analysis of variance (ANOVA) test is performed to determine if there is a significant difference in the LDDMM distances across the six different types of spines. The resulting p-value is 8.486×10^{-13}. This indicates that there is indeed a significant difference in the LDDMM distance between the double, flipodia, long mushroom, mushroom, stubby, and thin spines.

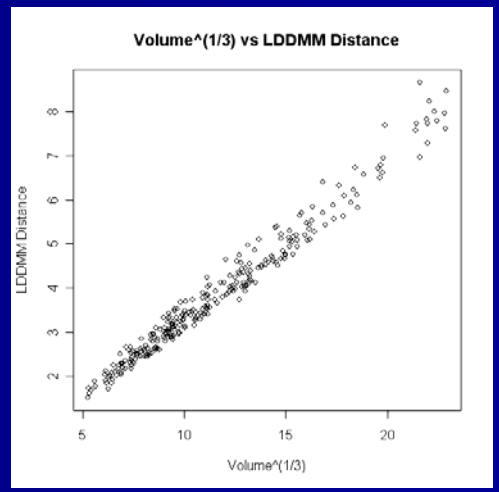


Analysis of Individual Variables: Volume

A linear model is constructed with volume as the predictor variable and the LDDMM distance as the response variable. The resulting adjusted R^2 value is 0.8874.

However, when volume$^{1/3}$ is used as the predictor variable, the new adjusted R^2 value is 0.9722. This indicates that volume$^{1/3}$ is a better predictor that the volume itself.

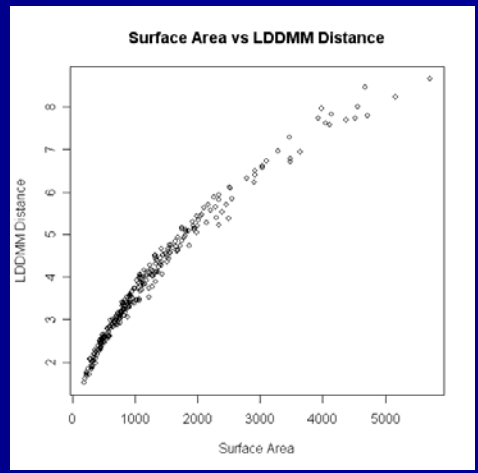


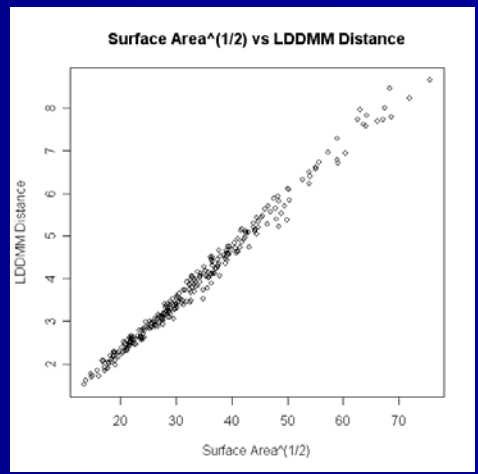


Analysis of Individual Variables: Surface Area

A linear model is constructed with surface area as the predictor variable and the LDDMM distance as the response variable. The resulting adjusted R^2 value is 0.9488.

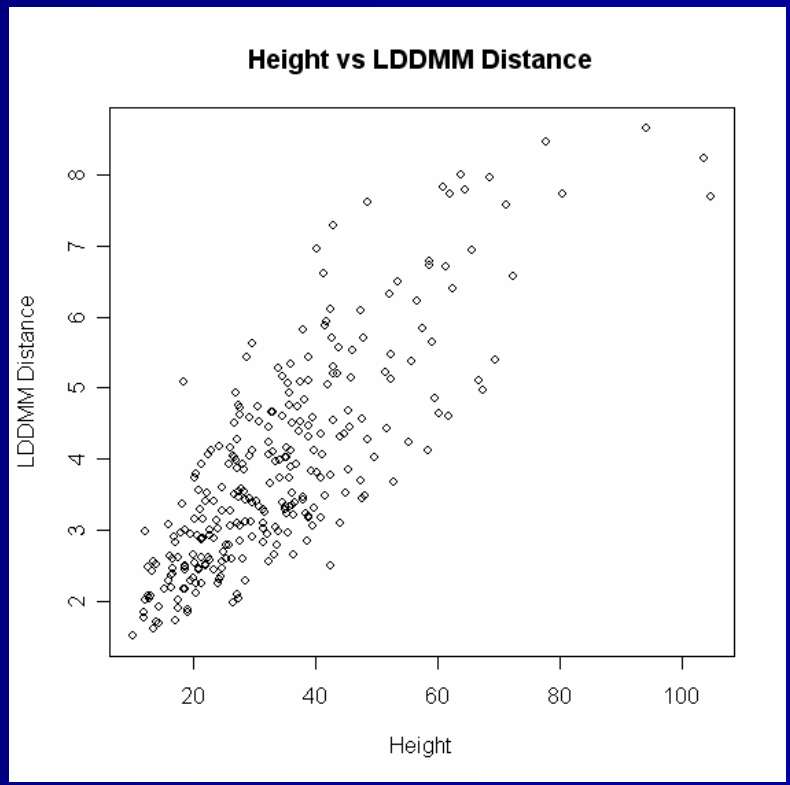
However, when surface area$^{1/2}$ is used as the predictor variable, the new adjusted R^2 value is 0.9893. This indicates that surface area$^{1/2}$ is a better predictor than the surface area itself.





Analysis of Individual Variables: Height

A linear model is constructed with height as the predictor variable and the LDDMM distance as the response variable. The resulting adjusted R^2 value is 0.6588.



Full Model

A linear model is constructed using condition, type, volume$^{1/3}$, surface area$^{1/2}$, and height as predictor variables and the LDDMM distance as the response variable. Only first order interactions are included for simplicity and interpretability of the model. The resulting adjusted R^2 value is 0.9958.

However, not all of the coefficients in the model are significant. Hence a model selection scheme is performed. We resort to backward elimination, removing one variable at a time until all the remaining variables are meaningful, significant, and the model has a considerably large R^2 value.

Model Selection (with Backward Elimination)

We first remove the interaction terms, one by one, because all of the estimates of the coefficients corresponding to the interactions have large p-values. After all of the interactions are removed, the adjusted R^2 value decreases (by only 0.0002) to 0.9956.

Next, we remove the type from the set of predictor variables since all of the estimates of the coefficients corresponding to type in the revised model have p-values over 0.6. As a result, the adjusted R^2 value remains the same at 0.9956.

In this new model, the estimate of the coefficient corresponding to the condition is the only coefficient left that is not significant. Hence, we remove condition from the set of predictor variables. The adjusted R^2 value still remains the same at 0.9956.

Final Model

The final model constructed contains volume$^{1/3}$, surface area$^{1/2}$, and height as predictors, without any interaction terms. The adjusted R^2 value is 0.9956. This indicates that almost all of the variation in the LDDMM distances can be explained by just volume$^{1/3}$, surface area$^{1/2}$, and height.

Final Model (cont.)

The final linear model is of the form:

$$Y_i = \beta_0 + \beta_1 * \sqrt[3]{X_i^{vol}} + \beta_2 * \sqrt{X_i^{sa}} + \beta_3 * X_i^{height} + \varepsilon_i$$

where Y_i is the LDDMM value of the i^{th} dendritc spine, X_i^{vol} is its volume, X_i^{sa} is its surface area, X_i^{height} is its height, and ε_i is the error term of the i^{th} spine.

Estimates of the coefficients in the final model, along with their p-values

coefficient	description	estimate	std. error	test statistic	p-value
β_0	intercept	-0.22996	0.01903	-12.08	$< 2.0 \times 10^{-16}$
β_1	coefficient of volume$^{1/3}$	0.12059	0.00685	17.61	$< 2.0 \times 10^{-16}$
β_2	coefficient of surface area$^{1/2}$	0.08091	0.00229	35.36	$< 2.0 \times 10^{-16}$
β_3	coefficient of height	0.00659	0.00099	6.628	1.77×10^{-10}

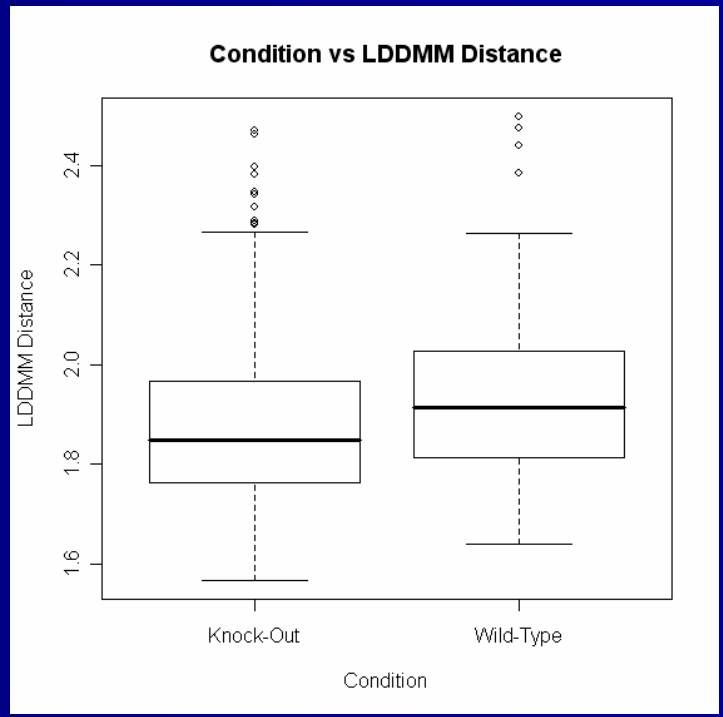
Conclusions

The results indicate that the size of the dendrites is having the largest effect upon the LDDMM distances since volume$^{1/3}$, surface area$^{1/2}$, and height are found to be the best predictors. The size differences may be masking the influence of other factors, such as the condition of mice.

Scaled Data: LDDMM and Condition

We perform a two-sample *t* test to determine if there is a significant difference in the scaled LDDMM distances between the two conditions. The resulting p-value is 0.01454. However, the *t* test assumes that the data is normally distributed, but in this case, normality fails.

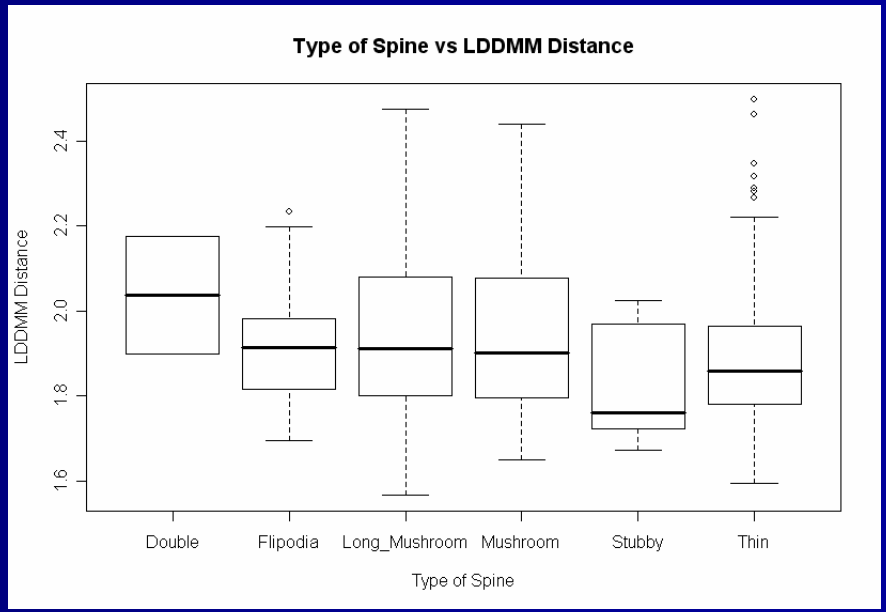
Hence, we perform a nonparametric test. The Wilcoxon rank sum test has a resulting p-value of 0.01028. This indicates that there is indeed a significant difference in the scaled LDDMM distances between the wild-type mice and the knock-out mice.



Scaled Data: LDDMM and Type of Spine

An analysis of variance (ANOVA) test is performed to determine if there is a significant difference in the LDDMM distances across the six different types of spines. The resulting p-value is 0.04785. However, the ANOVA test assumes that the data is normally distributed, but in this case, normality fails.

Hence, we perform a nonparametric test. The Kruskal-Wallis rank sum test has a resulting p-value of 0.0719. Thus, we cannot conclude that there is a significant difference in the LDDMM distances between the double, flipodia, long mushroom, mushroom, stubby, and thin spines.

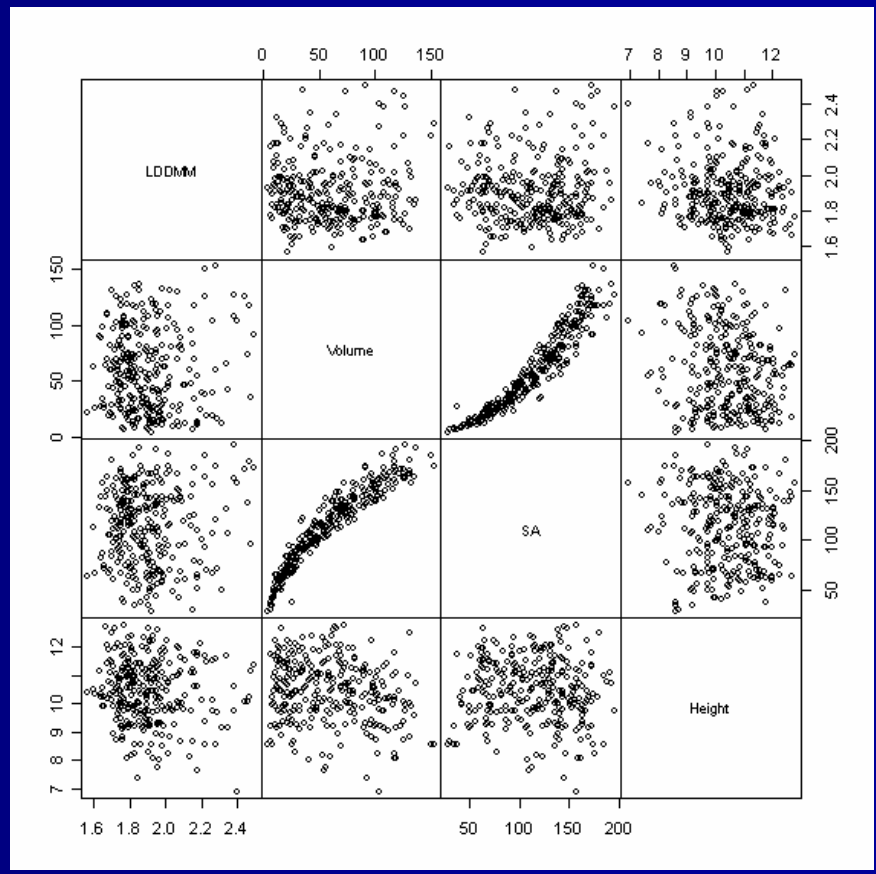


Scaled Data: Volume, Surface Area, and Height

Correlation Coefficients

	LDDMM	Volume	Surface Area	Height
LDDMM	1.0000	0.0349	0.0549	-0.0954
Volume	0.0349	1.0000	0.9484	-0.1896
Surface Area	0.0549	0.9484	1.0000	-0.0530
Height	-0.0954	-0.1896	-0.0530	1.0000

The graphs, along with the correlation coefficients, indicate that volume, surface area, and height are not good predictors for the scaled LDDMM distances.



ANOVA test for Multiple Regression: Unscaled and Scaled

An ANOVA test for multiple regression treats the variables successively; it calculates the significance of each variable after accounting for the influence of all the previous variables.

Unscaled Data

	Df	F value	P-value
Volume	1	5454.044	$< 2.2 \times 10^{-16}$
Surface Area	1	361.7470	$< 2.2 \times 10^{-16}$
Height	1	1.9260	0.1664
Type of Spine	5	11.3079	7.743×10^{-10}
Condition	1	0.5696	0.4511

Scaled Data

	Df	F value	P-value
Volume	1	0.9790	0.32341
Surface Area	1	0.2457	0.62057
Height	1	5.9363	0.01553
Type of Spine	5	2.0667	0.07015
Condition	1	4.9017	0.02774

With the unscaled data, the condition is not significant after the influence of the other variables is accounted for. However, in the scaled data, the condition is still significant after accounting for the volume, surface area, height, and type of spine.

Future Research

1. Further analysis of the scaled data

2. Analysis of dendritic spines afflicted with Parkinson's disease to determine if differences in LDDMM distances can be detected not only due to Fragile X syndrome, but also due to Parkinson's

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