Association of Brain Function and Structure with Neuropsychological Measures

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Introduction

This study aims to understand the association between brain white matter structure and neurocognitive measures associated with Hurler syndrome, a rare genetic disorder. In this study, we aim to utilize DTI metrics like fractional anisotropy (FA) and mean diffusivity (MD) to understand the brain's white matter integrity in correlation with neurocognitive scores in the study population. The research aims to explore if there is an association between these DTI measures and neurocognitive performance. The study also aims to find how this relationship may vary between patients with severe and attenuated forms of Hurler syndrome. This investigation is critical for providing insights into the neurological impacts of Hurler syndrome and the potential influence of treatment modalities on cognitive outcomes.

Dataset

The data contains 14 observations and 16 variables. The dataset includes information from clinic visits of patients with Hurler syndrome, categorized into severe and attenuated groups based on their clinical presentation and treatment history. Key variables include patient demographics like age, sex, and medical risk factors. DTI measures are the FA and MD variables, and the neurocognitive scores given in variables FSIQ(for IQ), CVLT(memory), JLO(Spatial Ability), and TOVA (attention) are also present in the dataset. The scores have been normalized to a mean of 100 and a standard deviation of 15.

Exploratory Data Analysis

Table 1: Summary Statistics by Group

Variable	Total	Severe Group	Attenuated Group
Number of Participants	14.000	7.000	7.000
Mean Age (months)	14.174	11.721	16.626
Age SD (months)	5.215	4.916	4.553
Percentage Male (%)	42.857	28.571	57.143
Percentage Female (%)	57.143	71.429	42.857
Mean FA	0.571	0.507	0.634
SD FA	0.105	0.110	0.049
Mean MD	1.045	1.129	0.961
SD MD	0.148	0.140	0.108
Mean TOVAd	77.500	70.571	84.429
SD TOVAd	12.623	6.528	13.806
Mean TOVA Omission Errors	70.214	58.429	82.000
SD TOVA Omission Errors	28.345	23.902	29.075
Mean TOVA Commission Errors	88.357	78.000	98.714
SD TOVA Commission Errors	22.438	26.758	11.161
Mean TOVA Response Time	92.929	88.286	97.571
SD TOVA Response Time	17.968	15.724	20.049
Mean TOVA Variability	79.286	69.714	88.857
SD TOVA Variability	24.078	14.580	28.806

The data contains 14 observations and 16 variables, with no missing data. Table 1 offers a detailed statistical summary of participants divided into two groups based on the severity of Hurler syndrome: severe and attenuated. In terms of demographics, the severe group has fewer males (29%) than the attenuated group (57%) and, conversely, more females (71%) than the attenuated group (43%). This gender disparity could potentially influence the results, given that gender-specific responses to treatment or disease progression are there in clinical studies. Age distribution shows that participants in the severe group are generally younger, with an average age of 11.70 months, compared to 16.60 months in the attenuated group. The standard deviations for age are relatively close (4.92 months for the severe group and 4.55 months for the attenuated group), indicating a similar age range within each group. Looking at the neurocognitive and DTI metrics, the average Fractional Anisotropy (FA) values are lower in the severe group (0.51 with a standard deviation of 0.11) than in the attenuated group (0.63 with a standard deviation of 0.05), suggesting better white matter integrity in the attenuated group.

Conversely, Mean Diffusivity (MD) values are higher in the severe group (1.13 with a standard deviation of 0.14) compared to the attenuated group (0.96 with a standard deviation of 0.11), typically indicating poorer white matter health in the severe group. There are notable differences between the groups for the neurocognitive scores measured by tests like TOVA. The severe group scores are lower across most measures, particularly noticeable in TOVAd scores (70.60 vs. 84.40), TOVAOm (58.40 vs. 82.00), and TovaVAR (69.70 vs. 88.90).

Figure 1 shows the relationships between brain white matter integrity, measured by Fractional Anisotropy (FA) and Mean Diffusivity (MD), and neurocognitive scores, represented by Full-Scale IQ (FSIQ) and California Verbal Learning Test (CVLT) scores, for patients with Hurler syndrome. The participants are differentiated into severe and attenuated groups, depicted by red and blue points, respectively. In the FA vs. FSIQ plot, there is a visible positive correlation for both patient groups, suggesting that higher FA values, which imply better organized white matter tracts, are associated with higher FSIQ scores, indicating better overall cognitive functioning. The slope for the attenuated group (blue points) appears steeper, indicating a potentially stronger association between FA and FSIQ scores than the severe group. Conversely, the MD vs. FSIQ plot shows a negative correlation, which is more in the severe group. Higher MD values indicate less restricted water diffusion and possibly less healthy white matter correspond to lower FSIQ scores. This suggests that white matter damage or disorganization could adversely affect cognitive function more in the severe group. There is no notable trend in the FA vs. CVLT plot, with data points scattered horizontally, suggesting no clear association between FA values and memory scores measured by the CVLT. The MD vs. CVLT plot also reflects a lack of evident correlation. Both severe and attenuated groups do not display any noticeable pattern indicating a relationship between mean diffusivity and verbal learning capabilities.

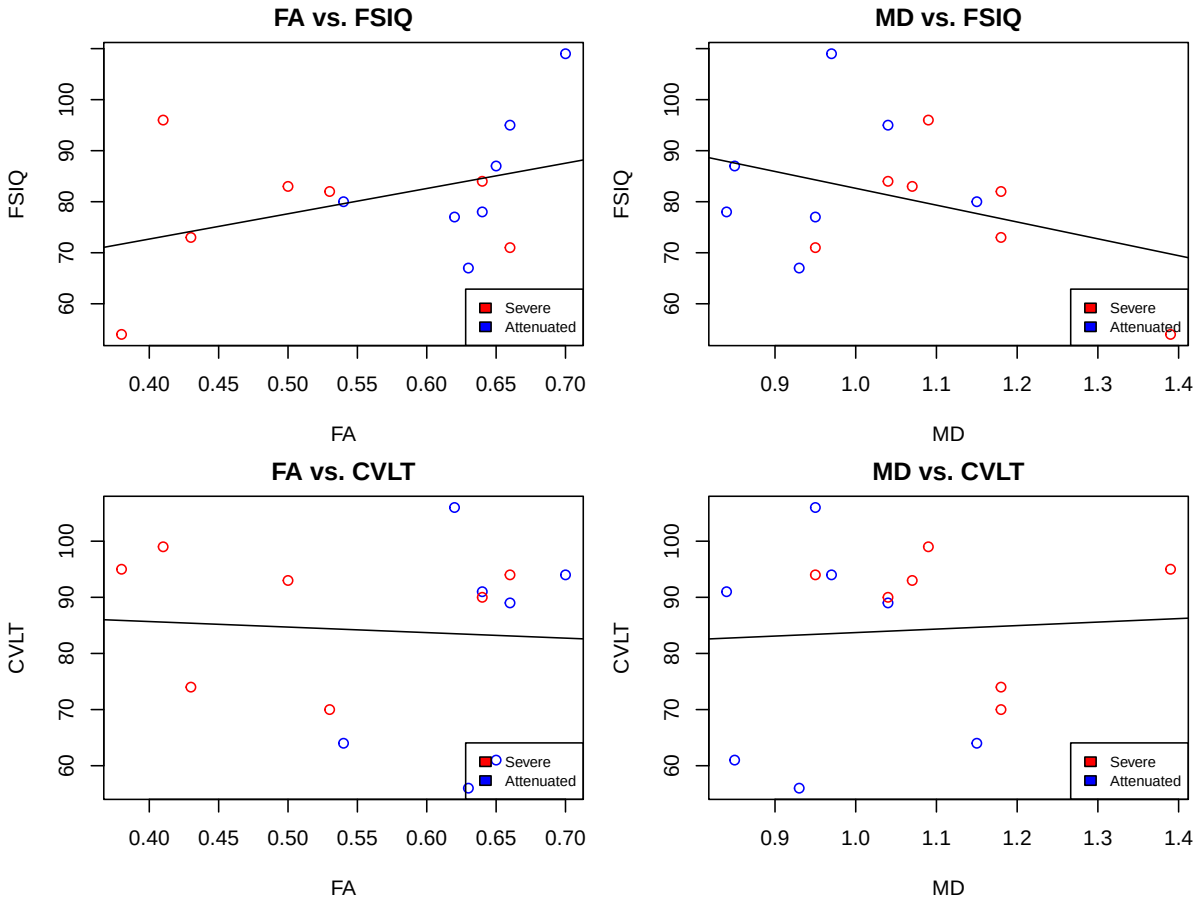


Figure 2 shows the series of Q-Q (quantile-quantile) plots used to evaluate the normality of the distributions of various variables, segmented by group (severe and Attenuated). Each plot corresponds to a different combination of neurocognitive score and Diffusion Tensor Imaging (DTI) measure (either FA or MD) for both groups of patients with Hurler syndrome. The horizontal axis shows the theoretical quantiles of a normal distribution, while the vertical axis shows the observed quantiles of the dataset for each measure: FA, MD, FSIQ, CVLT, TOVA d-prime, TOVA omissions, TOVA commissions, TOVA reaction time, and TOVA variability scores. Both FA and MD Q-Q plots for the severe and attenuated groups show points that generally follow the line, indicating normal distribution, with slight deviations, particularly at the ends. This suggests that FA and MD values for both groups are approximately normally distributed with potential outliers or extreme values. The FSIQ, CVLT, and various TOVA score Q-Q plots for both groups also largely follow the expected line, especially in the middle range of the data, which suggests that the central portions of these distributions are consistent with a normal distribution. JLO and TOVAOm show a significant deviation from a normal distribution. I have conducted the Shapiro-Wilk test for normality, and the results in Table 2. support the findings in the QQ plot.

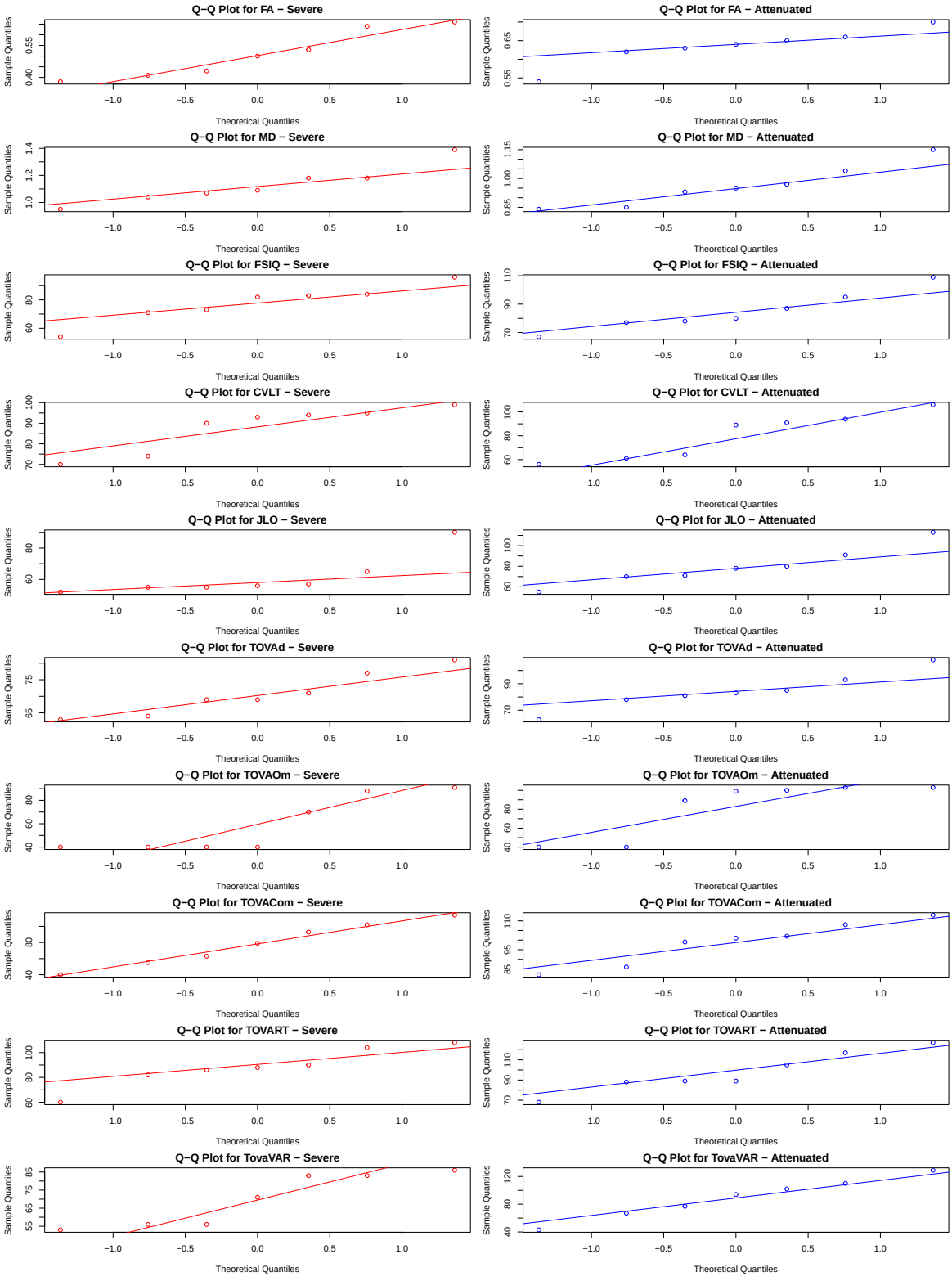
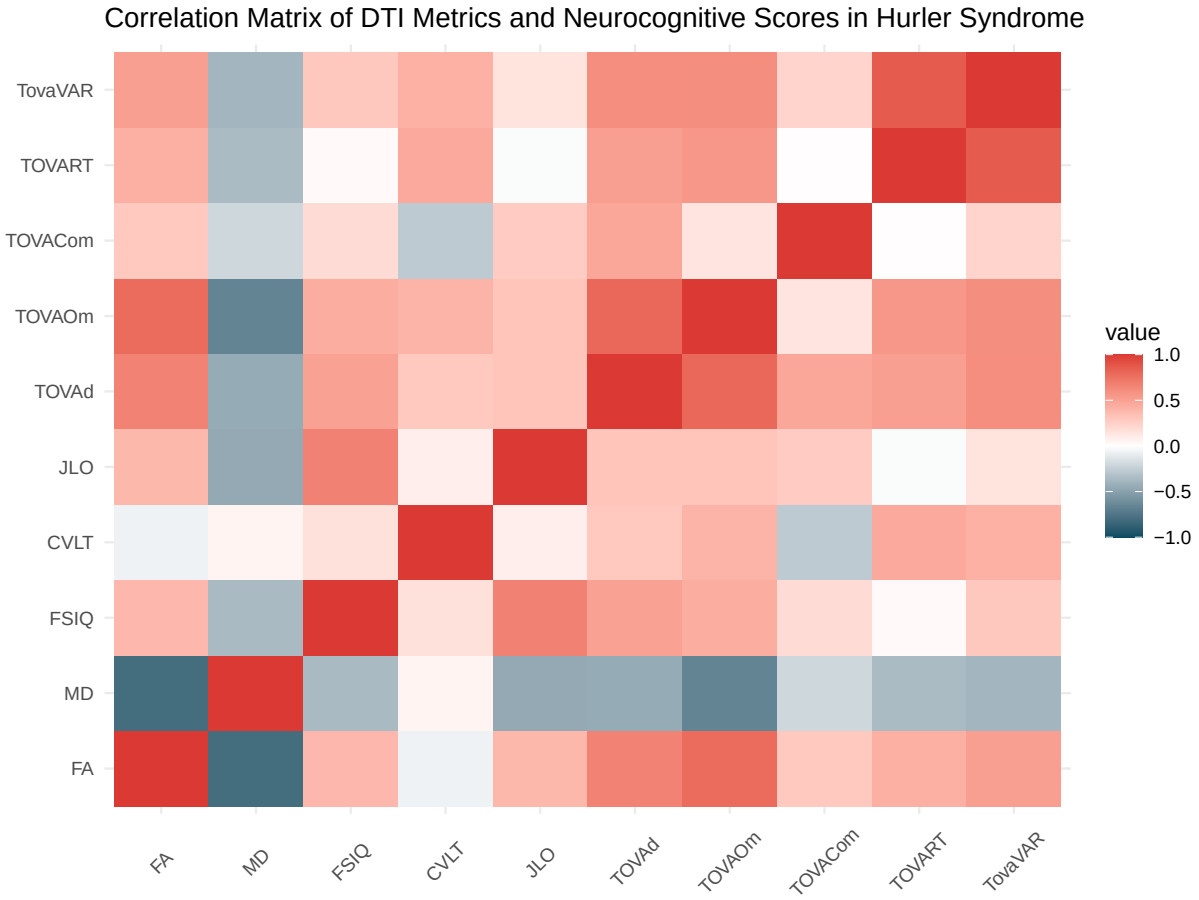

Q−Q Plot for FA − Severe
Q−Q Plot for FA − Attenuated
Q−Q Plot for MD − Severe
Q−Q Plot for MD − Attenuated
Q−Q Plot for FSIQ − Severe
Q−Q Plot for FSIQ − Attenuated
Q−Q Plot for CVLT − Severe
Q−Q Plot for CVLT − Attenuated
Q−Q Plot for JLO − Severe
Q−Q Plot for JLO − Attenuated
Q−Q Plot for TOVAd − Severe
Q−Q Plot for TOVAd − Attenuated
Q−Q Plot for TOVAOm − Severe
Q−Q Plot for TOVAOm − Attenuated
Q−Q Plot for TOVACom − Severe
Q−Q Plot for TOVACom − Attenuated
Q−Q Plot for TOVART − Severe
Q−Q Plot for TOVART − Attenuated
Q−Q Plot for TovaVAR − Severe
Q−Q Plot for TovaVAR − Attenuated
Sample Quantiles
Theoretical Quantiles

Figure 3. shows a correlation matrix heatmap, providing insights into the relationships between various neurocognitive scores and Diffusion Tensor Imaging (DTI) metrics, specifically Fractional Anisotropy (FA) and Mean Diffusivity (MD), in individuals diagnosed with Hurler Syndrome. The darker shades of red indicate stronger positive correlations, and darker shades of blue signify stronger negative correlations, indicating that the other tends to decrease as one variable increases. Lighter shades of red, blue, or white suggest weaker or insignificant linear relationships between the variables. Varying degrees of positive correlations are evident between FA and cognitive scores, whereas MD exhibits a mix of positive and negative correlations with neurocognitive scores.



Methods

In this study, we employed separate linear regression models to investigate the relationship between diffusion tensor imaging (DTI) metrics (specifically fractional anisotropy, FA, and mean diffusivity, MD) and various neurocognitive outcome variables. These outcome variables included Full-Scale Intelligence Quotient (FSIQ), California Verbal Learning Test (CVLT), Judgment of Line Orientation (JLO), and Test of Variables of Attention (TOVA) sub-scores. For each DTI metric (FA and MD), we defined multiple regression models to examine its association with each neurocognitive outcome variable. The models were structured to include the DTI metric, disease severity (Group), their interaction (DTI metric × Group), as well as covariates such as age, sex, and medical risk factors. For FA, the models were named according to the neurocognitive outcome variable being investigated (e.g., FSIQ_FA, CVLT_FA, etc.), while for MD, similar models were defined with the suffix "_MD" (e.g., FSIQ_MD, CVLT_MD, etc.). This approach allowed us to explore how FA and MD, individually, influence neurocognitive functioning across different cognitive domains while also considering the moderating effect of disease severity. Additionally, by accounting for potential confounding factors, we aimed to ensure the robustness and validity of our findings. The statistical significance of the regression coefficients was determined using p-values with an alpha of 0.05. The R-squared (R^2) and adjusted R-squared (adj. R^2) values are used to examine the adequacy of model fit. We performed diagnostic checks to ensure that our models met the assumptions of linear regression. These

checks included assessing linearity, independence of errors, homoscedasticity (constant variance of errors), and normality of residuals. We employed various diagnostic plots, such as scatterplots of observed vs. predicted values and residuals vs. fitted values, to inspect the model's adherence to these assumptions visually. Additionally, we calculated the Variance Inflation Factor (VIF) to identify and address multicollinearity issues if present. Statistical analysis was conducted using R Studio 4.3.3

Results

Table 2: Combined FA and MD Model Summaries

Predictor	Coefficient	Standard Error	t-value	p-value	Model_Name	R-squared	Adjusted R-squared
(Intercept)	-145.407	123.099	-1.181	0.276	FSIQ_FA	0.631	0.314
FA	403.035	200.805	2.007	0.085			
Group	118.402	63.830	1.855	0.106			
AGE..mo.	-1.524	0.894	-1.705	0.132			
Sexmale	13.309	7.131	1.866	0.104			
Medical.Risk.Factors	-1.980	4.261	-0.465	0.656			
FA:Group	-198.496	103.628	-1.915	0.097			
(Intercept)	-129.952	202.708	-0.641	0.542	CVLT_FA	0.265	-0.365
FA	347.967	330.668	1.052	0.328			
Group	116.822	105.110	1.111	0.303			
AGE..mo.	-1.009	1.472	-0.685	0.515			
Sexmale	1.727	11.743	0.147	0.887			
Medical.Risk.Factors	-2.029	7.017	-0.289	0.781			
FA:Group	-175.562	170.645	-1.029	0.338			
(Intercept)	-237.009	183.339	-1.293	0.237	JLO_FA	0.542	0.15
FA	535.328	299.073	1.790	0.117			
Group	163.218	95.067	1.717	0.130			
AGE..mo.	-0.293	1.332	-0.220	0.832			
Sexmale	8.011	10.621	0.754	0.475			
Medical.Risk.Factors	-1.091	6.347	-0.172	0.868			
FA:Group	-292.599	154.339	-1.896	0.100			
(Intercept)	11.402	129.240	0.088	0.932	TOVAd_FA	0.534	0.135
FA	129.928	210.823	0.616	0.557			
Group	17.086	67.015	0.255	0.806			
AGE..mo.	-0.345	0.939	-0.368	0.724			
Sexmale	6.601	7.487	0.882	0.407			
Medical.Risk.Factors	0.376	4.474	0.084	0.935			
FA:Group	-38.718	108.797	-0.356	0.732			
(Intercept)	-317.749	236.363	-1.344	0.221	TOVAOm_FA	0.691	0.426
FA	625.530	385.567	1.622	0.149			
Group	149.349	122.561	1.219	0.262			
AGE..mo.	-0.140	1.717	-0.082	0.937			
Sexmale	8.111	13.693	0.592	0.572			
Medical.Risk.Factors	-2.244	8.182	-0.274	0.792			
FA:Group	-233.880	198.976	-1.175	0.278			
(Intercept)	66.298	185.831	0.357	0.732	TOVACom_FA	0.695	0.434
FA	129.266	303.137	0.426	0.683			
Group	-48.134	96.359	-0.500	0.633			
AGE..mo.	-1.780	1.350	-1.319	0.229			
Sexmale	10.536	10.766	0.979	0.360			
Medical.Risk.Factors	20.729	6.433	3.222	0.015			
FA:Group	30.220	156.437	0.193	0.852			
(Intercept)	323.668	202.696	1.597	0.154	TOVART_FA	0.435	-0.05
FA	-338.139	330.647	-1.023	0.341			
Group	-138.241	105.104	-1.315	0.230			
AGE..mo.	-0.786	1.472	-0.534	0.610			

Predictor	Coefficient	Standard Error	t-value	p-value	Model_Name	R-squared	Adjusted R-squared
Sexmale	-3.053	11.743	-0.260	0.802			
Medical.Risk.Factors	-2.914	7.017	-0.415	0.690			
FA:Group	223.638	170.634	1.311	0.231			
(Intercept)	139.154	226.096	0.615	0.558	TovaVAR_FA	0.608	0.272
FA	31.666	368.820	0.086	0.934			
Group	-78.475	117.238	-0.669	0.525			
AGE..mo.	-3.600	1.642	-2.192	0.064			
Sexmale	3.987	13.098	0.304	0.770			
Medical.Risk.Factors	6.252	7.827	0.799	0.451			
FA:Group	102.117	190.333	0.537	0.608			
(Intercept)	102.133	141.481	0.722	0.494	FSIQ_MD	0.423	-0.071
MD	-3.881	138.398	-0.028	0.978			
Group	1.090	86.684	0.013	0.990			
AGE..mo.	-1.025	1.010	-1.015	0.344			
Sexmale	11.641	10.783	1.080	0.316			
Medical.Risk.Factors	-3.081	4.944	-0.623	0.553			
MD:Group	-4.108	84.354	-0.049	0.963			
(Intercept)	125.714	199.881	0.629	0.549	CVLT_MD	0.156	-0.568
MD	-43.530	195.526	-0.223	0.830			
Group	-20.564	122.465	-0.168	0.871			
AGE..mo.	-0.706	1.427	-0.495	0.636			
Sexmale	2.299	15.234	0.151	0.884			
Medical.Risk.Factors	-3.665	6.985	-0.525	0.616			
MD:Group	28.910	119.173	0.243	0.815			
(Intercept)	196.732	200.969	0.979	0.360	JLO_MD	0.35	-0.208
MD	-105.422	196.590	-0.536	0.608			
Group	-60.600	123.132	-0.492	0.638			
AGE..mo.	-0.314	1.435	-0.219	0.833			
Sexmale	9.881	15.317	0.645	0.539			
Medical.Risk.Factors	1.133	7.023	0.161	0.876			
MD:Group	46.123	119.822	0.385	0.712			
(Intercept)	14.783	124.223	0.119	0.909	TOVAd_MD	0.491	0.056
MD	70.759	121.516	0.582	0.579			
Group	35.536	76.110	0.467	0.655			
AGE..mo.	0.351	0.887	0.395	0.704			
Sexmale	3.029	9.468	0.320	0.758			
Medical.Risk.Factors	-2.499	4.341	-0.576	0.583			
MD:Group	-42.773	74.064	-0.578	0.582			
(Intercept)	224.955	254.421	0.884	0.406	TOVAOm_MD	0.577	0.214
MD	-176.623	248.878	-0.710	0.501			
Group	-58.135	155.882	-0.373	0.720			
AGE..mo.	1.078	1.816	0.594	0.571			
Sexmale	12.640	19.391	0.652	0.535			
Medical.Risk.Factors	-7.018	8.891	-0.789	0.456			
MD:Group	63.290	151.691	0.417	0.689			
(Intercept)	-27.458	178.619	-0.154	0.882	TOVACom_MD	0.667	0.382
MD	152.116	174.727	0.871	0.413			
Group	113.987	109.439	1.042	0.332			
AGE..mo.	-0.135	1.275	-0.106	0.919			
Sexmale	2.299	13.614	0.169	0.871			
Medical.Risk.Factors	17.659	6.242	2.829	0.025			
MD:Group	-141.107	106.496	-1.325	0.227			
(Intercept)	44.498	213.502	0.208	0.841	TOVART_MD	0.259	-0.377
MD	64.610	208.850	0.309	0.766			
Group	41.933	130.811	0.321	0.758			
AGE..mo.	-0.313	1.524	-0.206	0.843			
Sexmale	-4.391	16.273	-0.270	0.795			
Medical.Risk.Factors	-5.954	7.461	-0.798	0.451			

Predictor	Coefficient	Standard Error	t-value	p-value	Model_Name	R-squared	Adjusted R-squared
MD:Group	-44.111	127.294	-0.347	0.739			
(Intercept)	87.944	262.940	0.334	0.748	TovaVAR_MD	0.374	-0.163
MD	50.701	257.211	0.197	0.849			
Group	29.272	161.101	0.182	0.861			
AGE..mo.	-1.897	1.877	-1.011	0.346			
Sexmale	1.736	20.041	0.087	0.933			
Medical.Risk.Factors	-2.708	9.189	-0.295	0.777			
MD:Group	-48.016	156.770	-0.306	0.768			

Table 2. shows the linear regression analyses examining the associations between diffusion tensor imaging (DTI) metrics—fractional anisotropy (FA) and mean diffusivity (MD)—and various neurocognitive outcomes across different disease severity groups have been summarized. The results predominantly indicated that both main effects and interaction terms for FA and MD did not reach statistical significance, with most p-values exceeding the 0.05 threshold. This suggests that neither FA nor MD, nor their interactions with different groups, significantly predict the outcomes across the models studied.

However, specific analyses did reveal some associations of note, though these were not uniformly statistically significant. For fractional anisotropy (FA), a notable positive effect was observed for full-scale IQ (FSIQ) with an estimate of 403.03 and a standard error of 200.81, resulting in a t-value of 2.01 and a marginally significant p-value of 0.08. The interaction term between FA and group showed a negative trend for FSIQ, though it was marginally significant (= -198.50, SE = 103.63, t = -1.92, p = 0.10). Additionally, FA showed a positive, though not significant, influence on Judgment of Line Orientation (JLO) scores (= 535.33, SE = 299.07, t = 1.79, p = 0.12), with the FA:Group interaction term also indicating a negative trend (= -292.60, SE = 154.34, t = -1.90, p = 0.10). FSIQ displayed an R-squared of 0.63 and an adjusted R-squared of 0.31, indicating a moderate fit.

Mean diffusivity (MD) did not show significant effects on FSIQ or other cognitive tests. The only significant finding involving MD appeared in the Test of Variables of Attention (TOVA) concerning the impact of medical risk factors on commission errors in the TOVA Composite models for both FA and MD. In the TOVACom_FA model, medical risk factors were significantly predictive (= 20.73, SE = 6.43, t = 3.22, p = 0.01), explaining a substantial portion of variance with an R-squared of 0.70 and an adjusted R-squared of 0.43. Similarly, in the TOVACom_MD model, medical risk factors also proved significant (= 17.66, SE = 6.24, t = 2.83, p = 0.03) with an R-squared of 0.67 and an adjusted R-squared of 0.38.

These results indicate that while FA and MD generally do not significantly influence neurocognitive outcomes across different groups, medical risk factors consistently show a significant impact on the TOVA Composite scores, suggesting their strong influence independent of the diffusion measures.

Conclusions and Discussion

This study investigated the relationship between brain white matter structure, as quantified by diffusion tensor imaging (DTI) metrics fractional anisotropy (FA) and mean diffusivity (MD), and various neurocognitive measures in patients with Hurler syndrome. Despite the theoretical premise that DTI metrics would correlate with cognitive performance, reflecting the integrity of white matter pathways, the results predominantly indicated no significant association between these metrics and neurocognitive outcomes. The exception was found in the influence of medical risk factors, which showed significant effects in models for the TOVA Composite scores, suggesting that clinical severity and treatment history may have more profound impacts on certain cognitive outcomes than the microstructural properties of white matter. The analysis demonstrated that neither FA nor MD significantly predicted the neurocognitive scores across most tests, with R-squared values indicating modest explanatory power in the best scenarios. These findings highlight the complexity of brain-behavior relationships in Hurler syndrome and suggest that factors beyond simple DTI measures are influential, potentially encompassing genetic variability, environmental factors, and the nature of medical interventions.

The study's limitations are primarily related to its small sample size, which limits the statistical power and the generalizability of the findings. With only 14 participants, individual variability could disproportionately influence the results, and findings may not represent the broader population with Hurler syndrome. Additionally, the simplicity of using only two DTI metrics, fractional anisotropy and mean diffusivity, might not fully capture the complex brain pathology associated with the syndrome. The study's cross-sectional design only provides a snapshot in time, which is less informative of the dynamic nature of neurodevelopmental changes in pediatric conditions like Hurler syndrome. Potential confounding variables such as socioeconomic status, exact treatment regimens, and educational interventions were not controlled for,

which could also influence cognitive outcomes. These factors suggest the need for a cautious interpretation of the results and highlight the importance of further research with a more robust methodological approach.