White Matter and Language in Autism

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On behalf of, Rutsohn, J., Cetin, G., Forsen, E., Swanson, M., Shoba, M., Wolff, J., Elison, J.T., Shen, M., Botteron, K., Dager, S., Estes, A., Gerig, G., McKinstry, R., Pandey, J., Schultz, R., St. John, T., Styner, M., Truong, Y., Zwaigenbaum, L., Hazlett, H., Piven, J., & Girault, J. for the IBIS Network

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HUGE shout outs:

Dr. Jessica Girault, PhD

Dr. Joshua Rutsohn, PhD

More information about IBIS

Read the paper!

Language Use

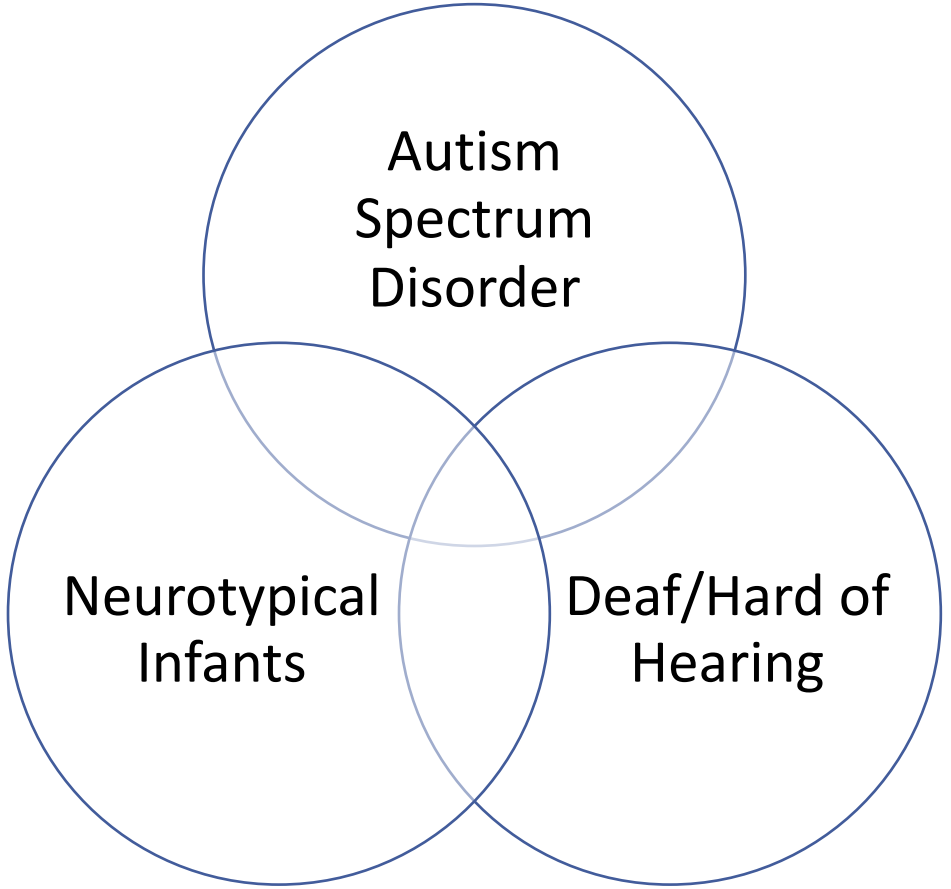
“High Likelihood”

“Autistic”

“infants with Autism Spectrum Disorder”

Respect, Gratitude, and Openness

Who are you and why this topic?



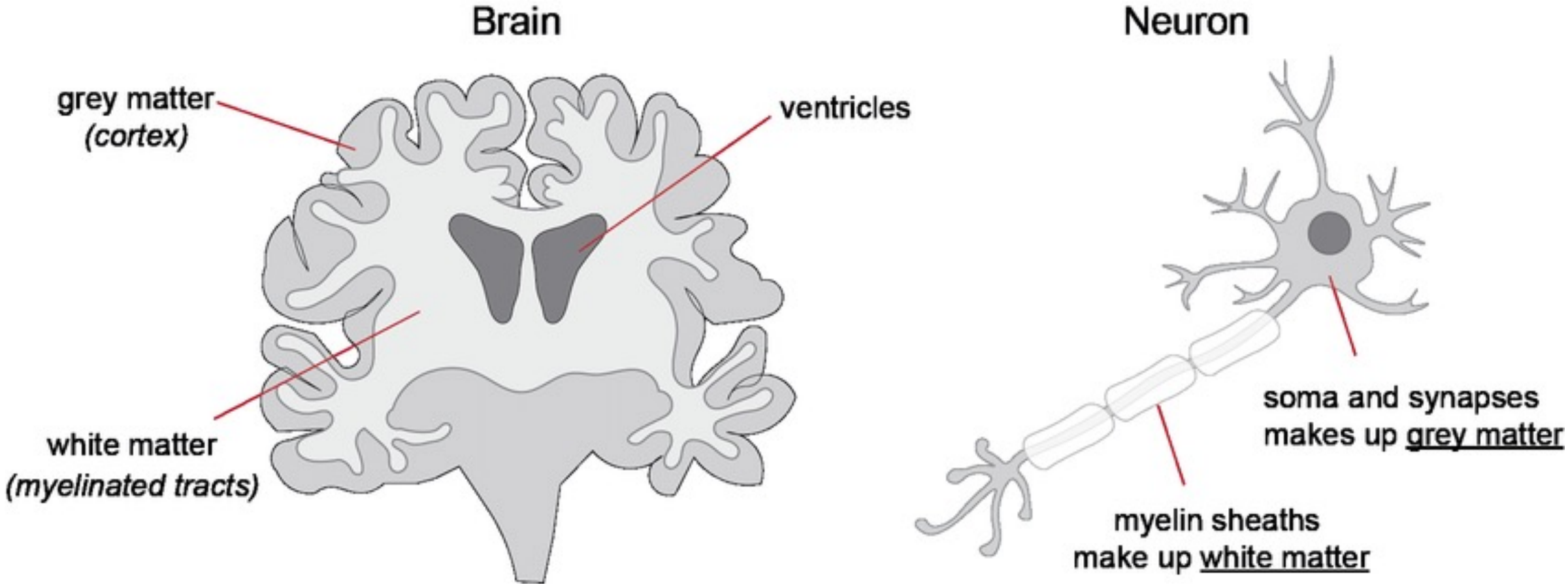
Background

- "Wait and see" model of language development
  - Sometimes this approach works!
  - Sometimes, we miss sensitive windows for supports

- Language delays are one of the earliest emerging endophenotypes of autism spectrum disorder
- Language delays in siblings of autistic youth (high likelihood siblings)
- Importance of neural circuity research → White matter

Koegel et al., 2014; Geschwind, 2008, Marrus et al., 2018, Viding & Blakemore, 2007

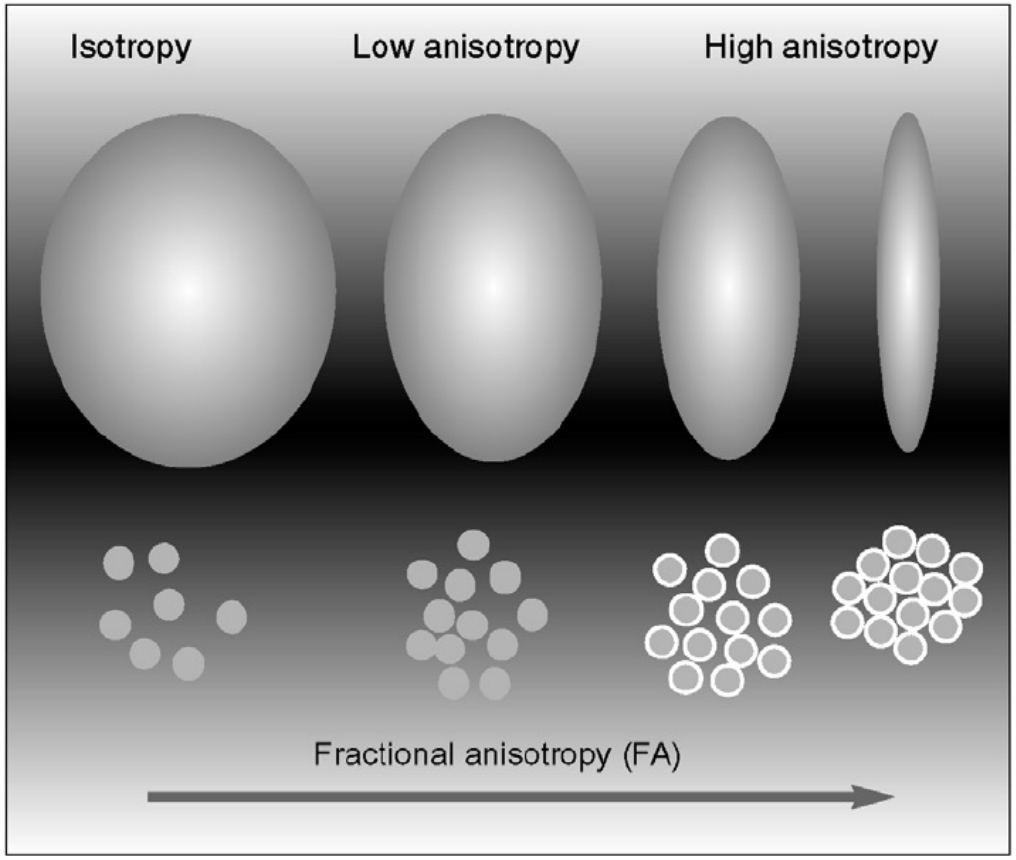
White Matter



Madden, 2020

White Matter

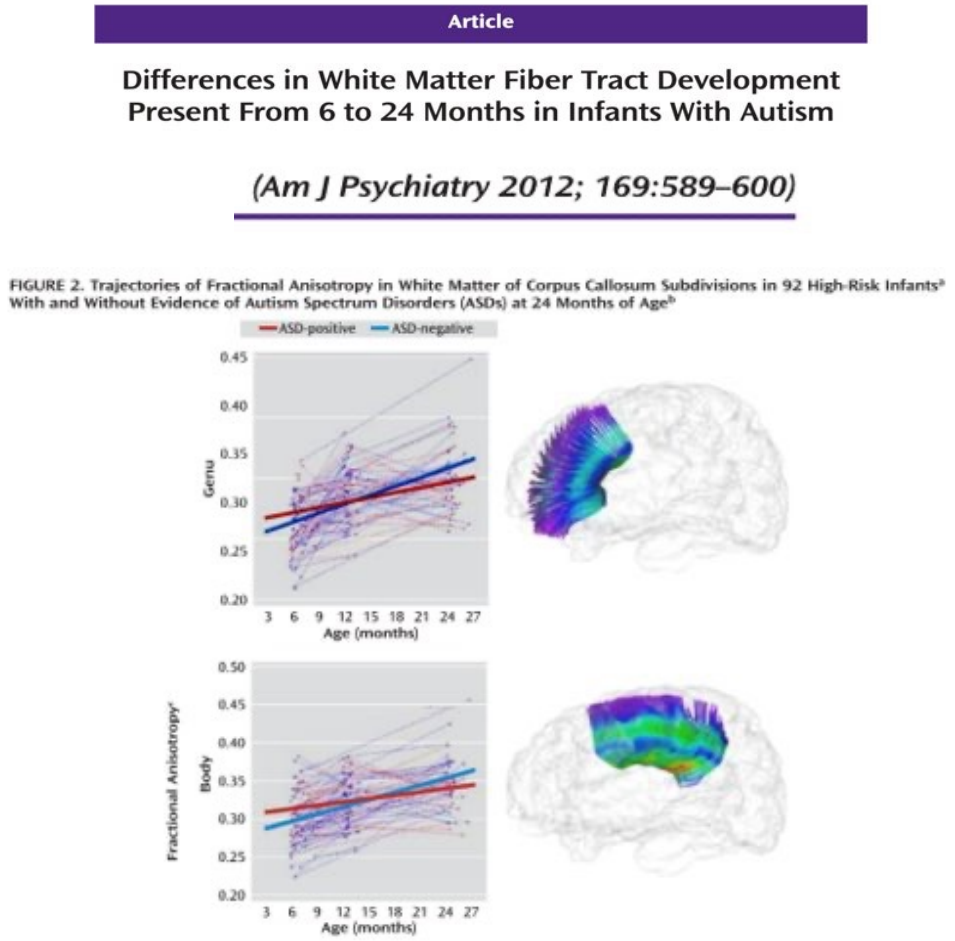
Baby poses for a picture in front of an MRI machine



Visual describing low to high FA

White Matter and ASD

- One of the earliest neural differences evidenced in ASD is atypical organization of white matter
- Evident by 6 months, persists through 24 months
- Behavioral implications
  - Social cognition
  - Behavioral control
  - Repetitive behaviors
  - Sensory interests


Article

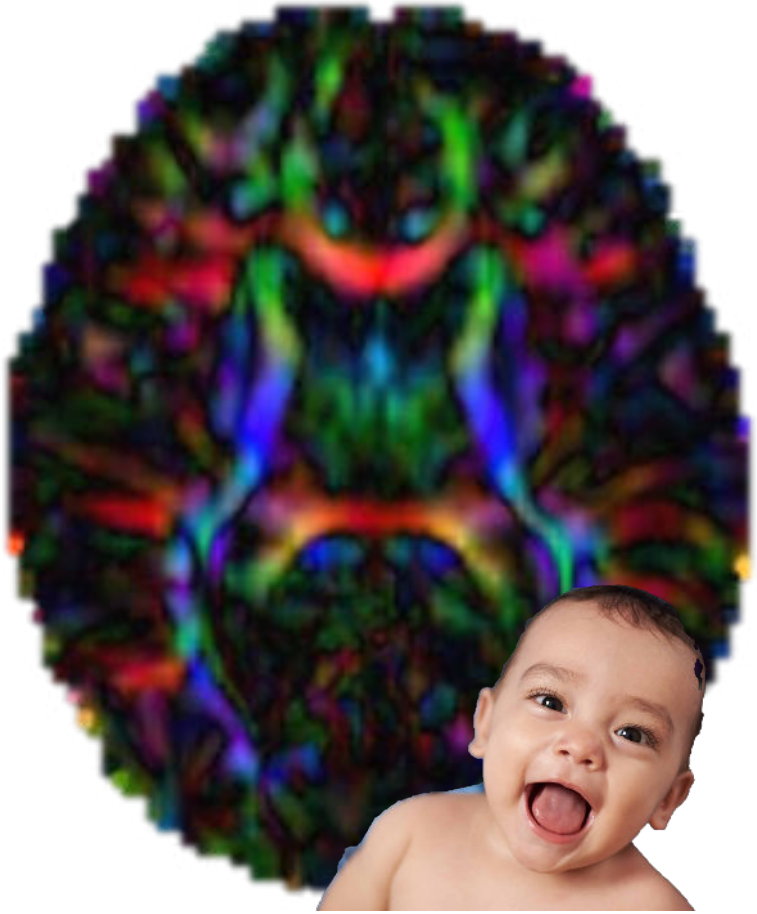
Differences in White Matter Fiber Tract Development Present From 6 to 24 Months in Infants With Autism

(Am J Psychiatry 2012; 169:589–600)

FIGURE 2. Trajectories of Fractional Anisotropy in White Matter of Corpus Callosum Subdivisions in 92 High-Risk Infants[a] With and Without Evidence of Autism Spectrum Disorders (ASDs) at 24 Months of Age[b]

Girault & Piven, 2020, Wolff et al., 2012, Wolff et al., 2015, Solso et al., 2016, Wolff et al., 2017

Importantly, despite white matter development coinciding with emerging language delays, no work has evaluated white matter and language in ASD during this developmental period



White Matter & Language

- WM --> cognitive ability, motor, language, visual reception in non-autistic toddlers
- Areas related to language: arcuate fasciculus, corpus callosum
  - Higher FA related to higher language levels
- Systematically evaluating the relationship between WM and language in ASD is imperative for understanding pathophysiology and informing language interventions

Girault et al., 2018, Sket et al., 2019, Swanson et al., 2021

Current Study

Goal: Evaluate longitudinal relationships between white matter microstructure and language in infants at HL and LL for ASD at 6, 12, and 24 months

Which white matter microstructures are related to expressive and receptive language in the first two postnatal years?

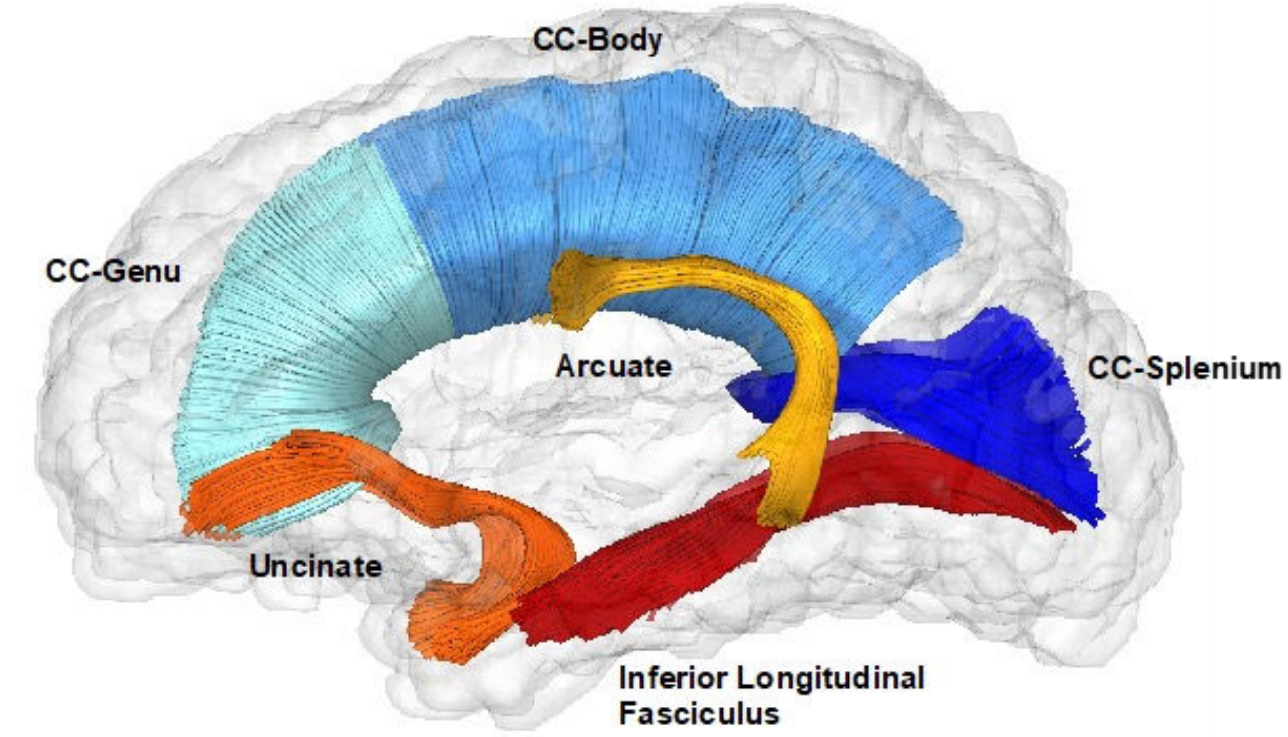
Do these relationships differ as a function of likelihood group?

If so, when?

The Infant Brain Imaging Study (IBIS)

- Follows infants at 6, 12, 24 months of age who have older siblings
- Some older siblings are neurotypical (LL siblings), some are autistic (HL-siblings)
  - It is anticipated that ~10-20% of HL siblings will go on to receive a diagnosis of ASD by 24 months
  - *"enriched"*
- This study is in its 15th year and has extended into school age

Method



Participants: *N* = 461

- HL-ASD (*n* = 70)
- HL-Neg (*n* = 251)
- LL-Neg (*n* = 140)

Measures:

- Mullen Expressive and Receptive age equivalents
- WM FA values from 9 tracts of interest

Analytic Plan

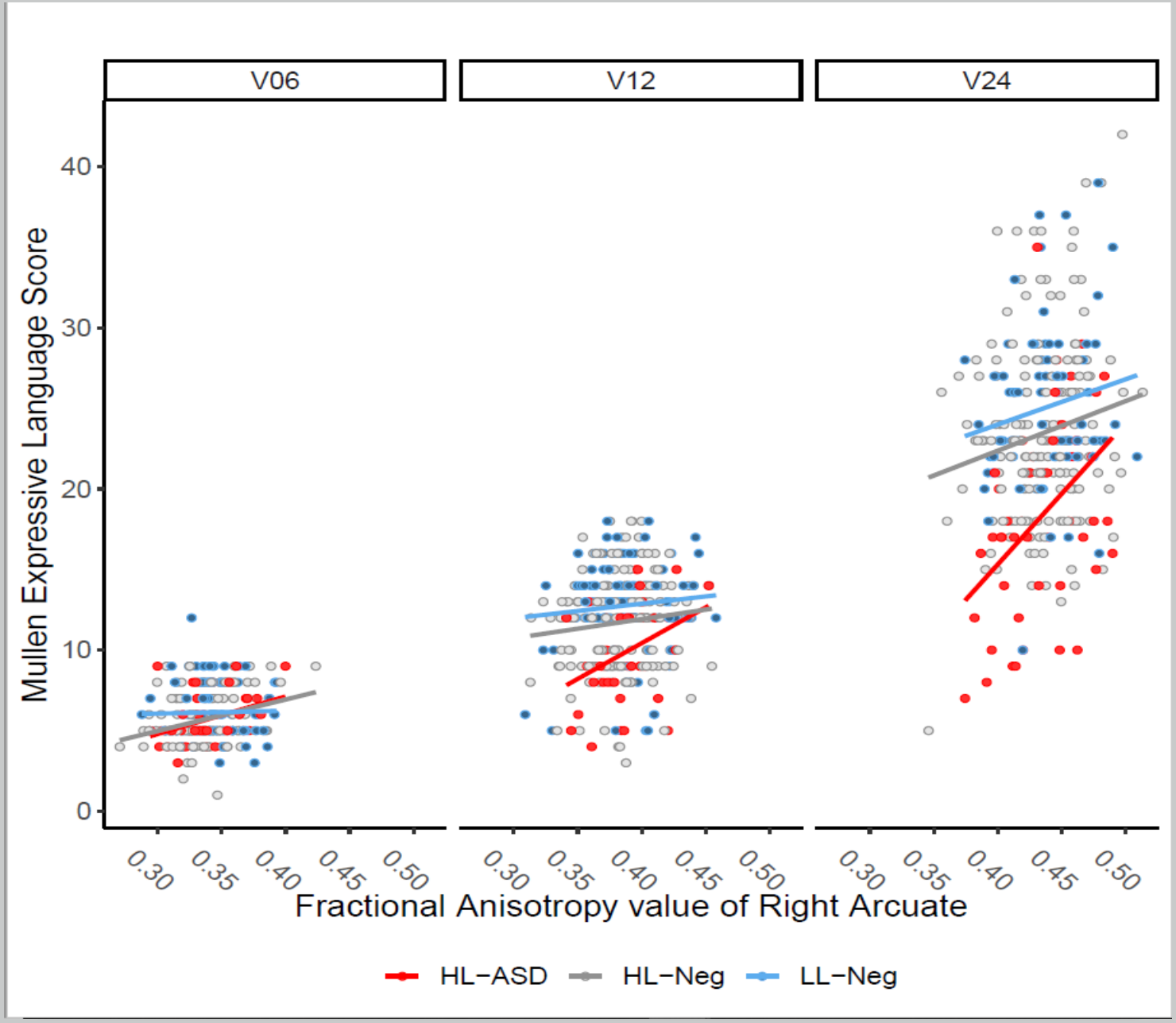
- Linear mixed effect models
- Fixed effects included group, microstructure, sex, piecewise linear estimates for 6-12 and 12-24 months, mother's education, recruitment site, and interaction terms
- Autoregressive correlation structure, missing data assumed MAR with multiple imputations
- Term of interest: FA x group

Results: Expressive Language -- Right Arcuate

	Left Arcuate	Right Arcuate	C.C. Body	C.C. Genu	C.C. Splenium	Left ILF	Right ILF	Left Uncinate	Right Uncinate
Intercept	-1.59	-2.737	1.335	2.157	6.046	2.723	0.837	2.768	1.4
EL: Negative	3.818	7.028*	-0.12	-0.748	-2.28	0.776	3.692	-0.117	1.317
LL: Negative	7.029	8.51*	2.413	-0.945	-3.205	1.126	5.63	-1.263	3.419
6- to 12-months	3.803	1.939	3.6	9.438**	4.704	5.534	2.563	7.838*	2.899
12- to 24-months	0.841	-0.841	2.665	-14.834*	-0.32	-4.551	6.087	-6.393	0.112
White Matter	1.987	2.411**	1.027	0.831	-0.153	0.715	1.243	0.78	1.252
Male	-0.172	-0.176	-0.155	-0.139	-0.144	-0.153	-0.155	-0.154	-0.153
Mother's Education: College+	0.065	0.125	0.089	0.06	0.087	0.104	0.111	0.127	0.12
Site 1	0.033	-0.007	0.082	0.054	0.048	0.002	0.006	0.024	-0.009
Site 2	-0.319	-0.367	-0.209	-0.307	-0.291	-0.351	-0.38	-0.33	-0.365
Site 3	1.248***	1.216***	1.302***	1.221***	1.257***	1.236***	1.222***	1.221***	1.18***
EL: Neg. x 6-12	2.034*	2.536***	1.524	1.328	1.225	1.577*	1.902*	1.464*	1.576*
LL: Neg x 6-12	2.853**	3.124***	2.159*	1.683*	1.504*	2.015**	2.466**	1.772*	2.16**
EL: Neg. x 12-24	1.947*	1.971*	1.856*	2.143*	2.019*	1.826*	1.947*	1.967*	1.96*
LL: Neg. x 12-24	2.572**	2.543*	2.524**	2.733**	2.719**	2.412*	2.604**	2.584**	2.574**
EL: Neg. x WM	-1.102	-2.105*	0.021	0.192	0.49	-0.226	-1.027	0.019	-0.425
LL: Neg. x WM	-1.898	-2.424*	-0.53	0.349	0.778	-0.219	-1.443	0.486	-0.965
6-12 x White Matter	0.013	0.44	0.185	-1.143	0.045	-0.231	0.44	-0.891	0.471
12-24 x White Matter	0.621	0.95	0.205	4.039**	0.752	1.916	-0.603	2.724	0.869

Plotting our data: Right Arcuate and Expressive Language

HL-ASD group shows early, positive relationship between FA and EL that diverges from LL-Neg (6 mos) and HL-Neg (12 mos)

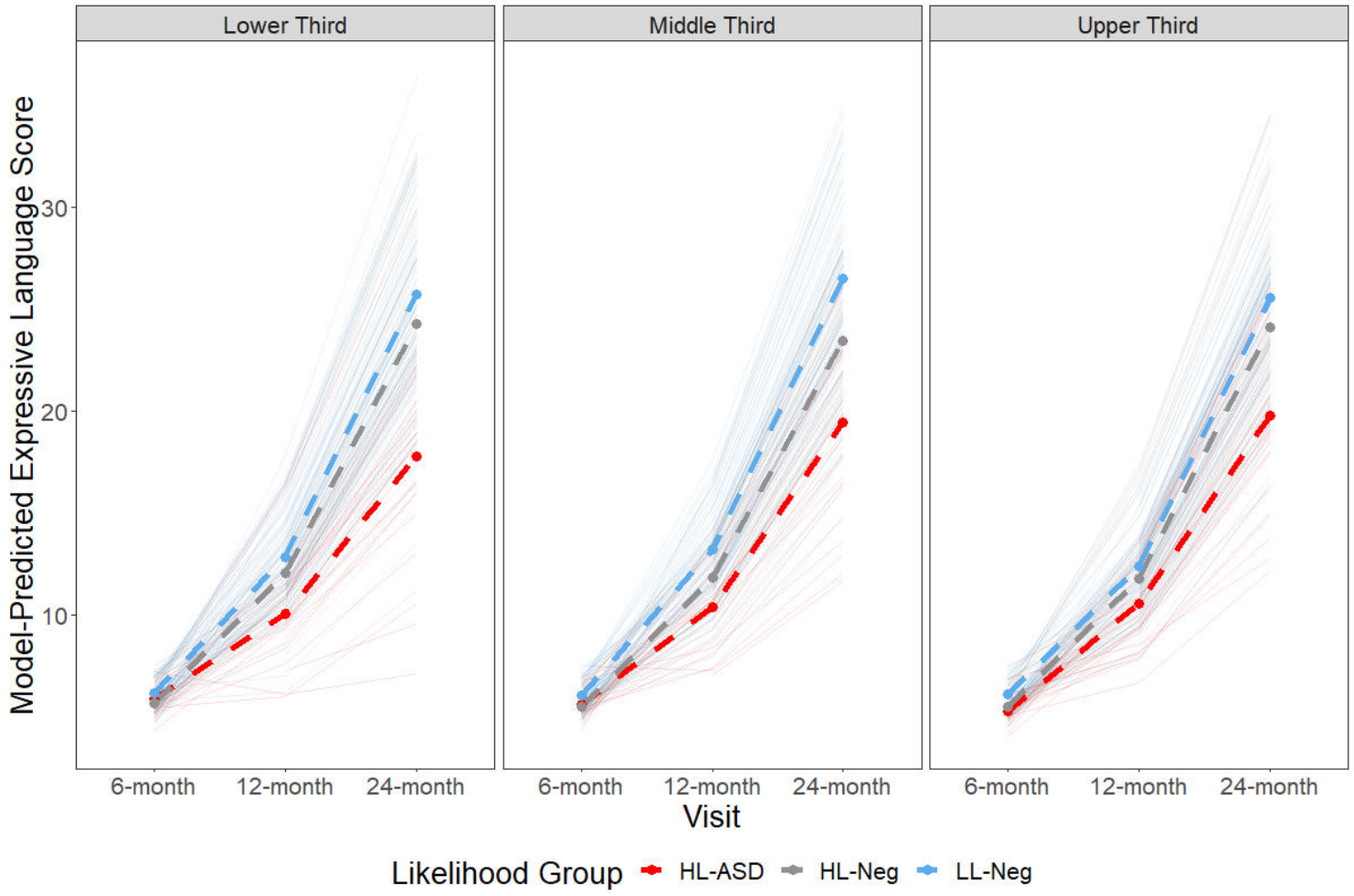


Model Predictions: EL and Right Arcuate

Mean trajectories of expressive language scores by likelihood group paneled by right arcuate FA percentiles

Similar trajectories observed for HL-Neg and LL-Neg samples across FA percentile groups.

HL-ASD group (red) has different slope and predicted language score at 24mos in lower and upper third FA percentile.

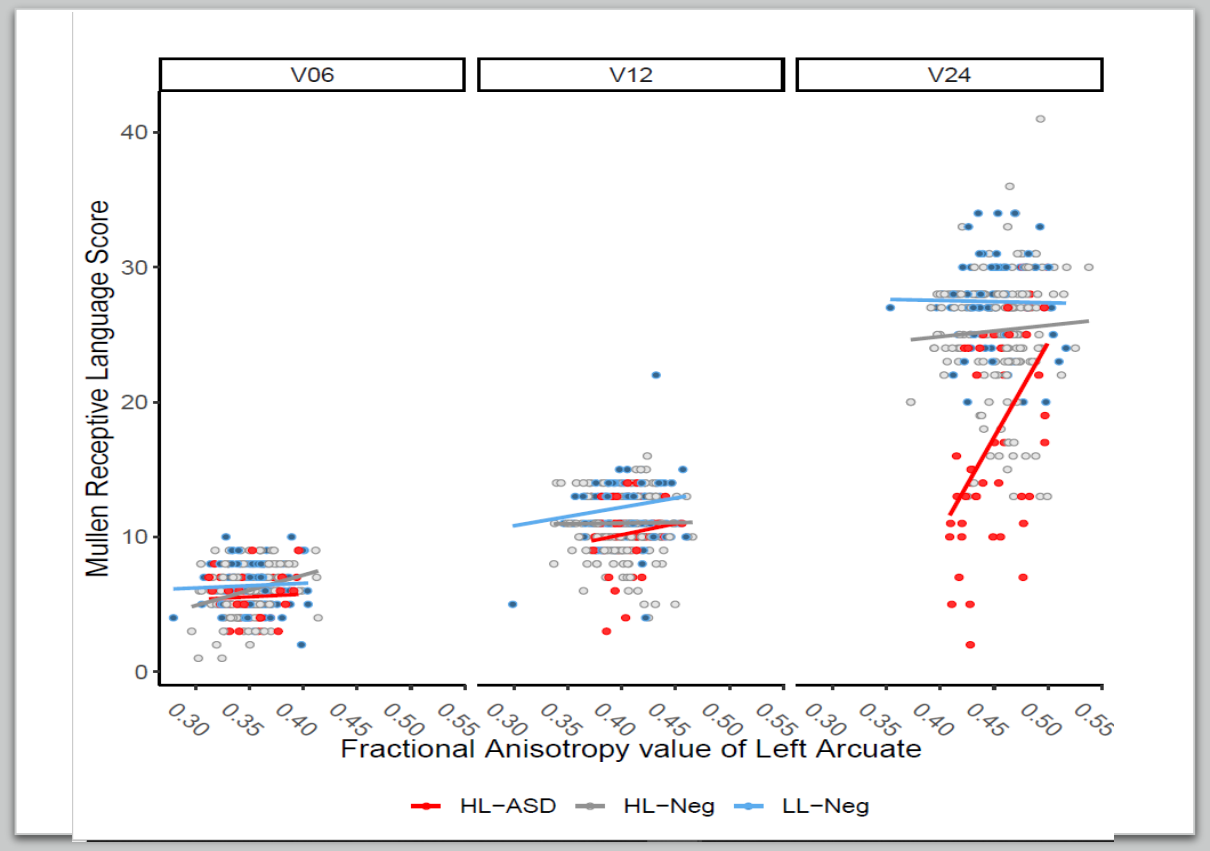


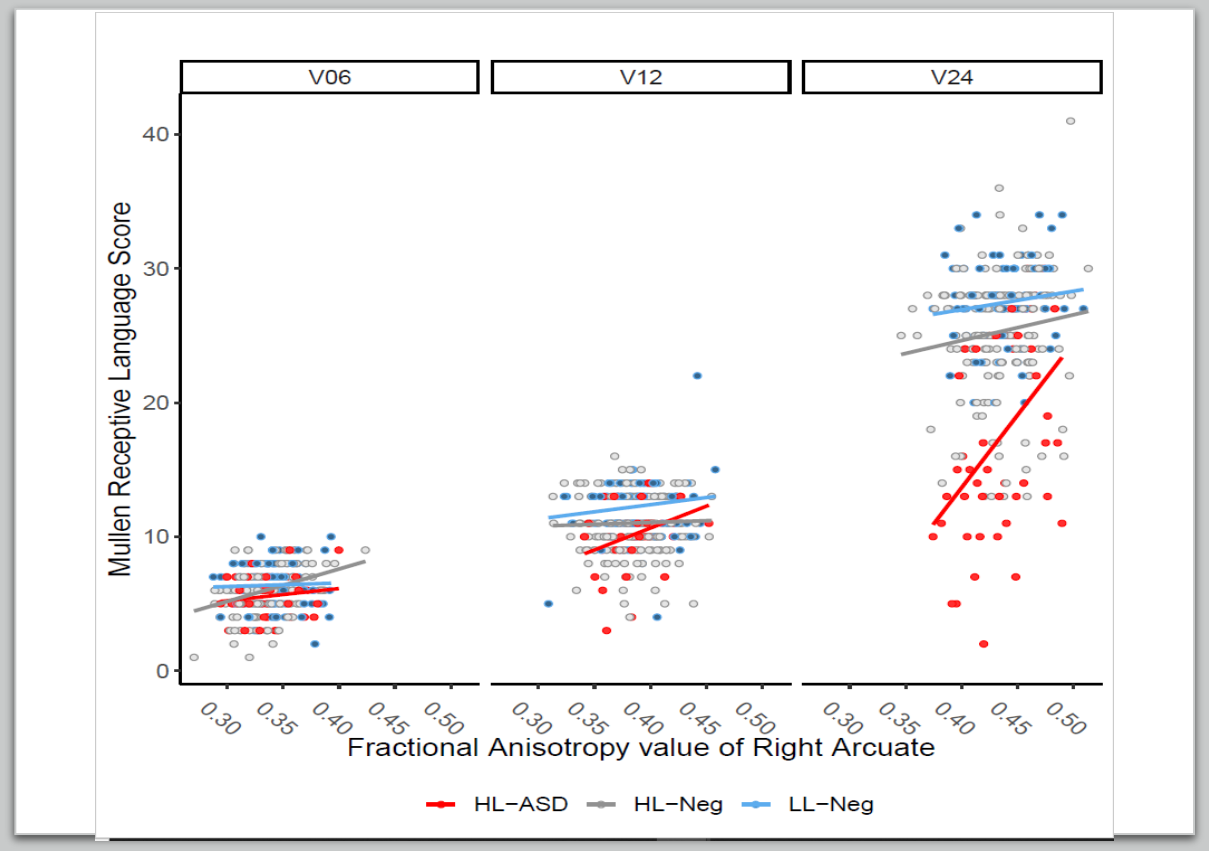
Results: Receptive Language – No Tracts

	Left Arcuate	Right Arcuate	C.C. Body	C.C. Genu	C.C. Splenium	Left ILF	Right ILF	Left Uncinate	Right Uncinate
Intercept	-0.649	-0.73	1.349	0.826	1.363	7.087**	1.883	4.931	3.671
EL: Negative	5.9	5.692	0.768	1.958	1.176	-3.091	1.765	-0.982	0.416
LL: Negative	7.975*	7.033	5.973	4.545	5.192	-0.236	4.506	1.512	1.717
6- to 12-months	3.853	4.454	5.036	7.631**	5.366*	4.99*	5.993	7.381*	5.682
12- to 24-months	-5.144	-3.378	2.604	-4.031	4.582	-0.498	1.493	-2.294	-1.835
White Matter	1.811	1.925	1.127	1.278	0.979	-0.353	1.063	0.248	0.653
Male	-0.2	-0.212	-0.19	-0.2	-0.207	-0.203	-0.203	-0.2	-0.196
Mother's Education: College+	0.035	0.043	-0.001	-0.009	-0.038	-0.004	0.012	0.022	0.027
Site 1	-0.19	-0.207	-0.15	-0.178	-0.186	-0.185	-0.193	-0.175	-0.198
Site 2	-1.037***	-1.047***	-0.951***	-1.017***	-0.96***	-1.042***	-1.054***	-1.042***	-1.042***
Site 3	1.283***	1.253***	1.326***	1.261***	1.3***	1.295***	1.265***	1.3***	1.265***
EL: Neg. x 6-12	1.645*	1.65*	0.925	1.023	0.922	0.566	1.025	0.75	0.849
LL: Neg x 6-12	2.701***	2.608**	2.214**	2.093*	2.147**	1.565*	2.089**	1.702*	1.737*
EL: Neg. x 12-24	5.746***	5.767***	5.702***	5.86***	5.787***	5.629***	5.733***	5.743***	5.745***
LL: Neg. x 12-24	6.078***	6.08***	6.123***	6.27***	5.958***	6.066***	6.085***	6.181***	6.099***
EL: Neg. x WM	-1.578	-1.59	-0.106	-0.411	-0.189	0.92	-0.394	0.395	-0.019
LL: Neg. x WM	-2.102	-1.92	-1.393	-1.023	-1.022	0.217	-1.077	-0.29	-0.36
6-12 x White Matter	-0.109	-0.286	-0.282	-0.903	-0.303	-0.138	-0.518	-0.875	-0.448
12-24 x White Matter	1.976	1.704	0.303	1.779	-0.09	0.993	0.604	1.692	1.564

Left and Right Arcuate and Receptive Language

- Both the L and R Arcuate had relationships between FA and Language that may warrant further exploration
- Same pattern of results as for expressive language: HL-ASD shows positive relationship between FA and language whereas other two groups show no relationship



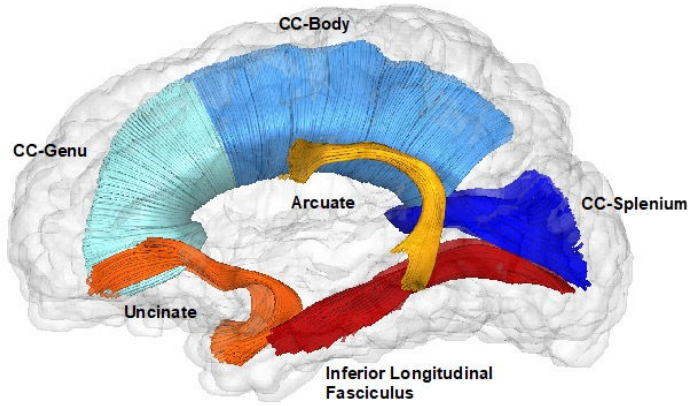


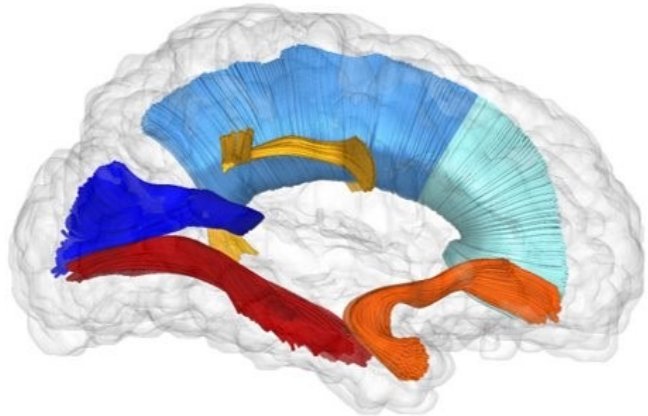
Summary

- Significant relationships between the WM Arcuate FA and language
  - Other WM tracts did not emerge as significant
  - Some differentiation between expressive and receptive language
  - These relationships were unique to language; no significant results emerged for NVI
- The relationship between language and the arcuate fasciculus is different in ASD compared to non-autistic controls
  - In ASD, strong positive relationship between WM FA and language emerges at 6-12 months and remains throughout 24 months
  - In non-ASD, WM FA and language relationships are not significant, or of smaller magnitude
  - HL-ASD infants with the least gains in FA values exhibited the least gains in language over time and overall lowest language scores by 24 months.

Discussion

- Findings specific to the Right Arcuate
  - L and R regions were not homologous in tractography
  - Some evidence suggesting left lateralization in the arcuate does not happen to the same extent in ASD
  - Could reflect right-dominant language processes, such as prosody
- Why only the arcuate?
  - Although other studies have linked FA to language in the splenium and corpus callosum across this same developmental period in non-autistic toddlers, we did not find these relationships, even in the LL sample





Fletcher et al., 2010, Flagg et al., 2005, Cermak et al., 2022, Swanson et al., 2015, Sket et al., 2019, Estes et al., 2015, Swason et al., 2017, Fusaroli, 2017

Future Directions

- Denser developmental sampling to understand more about the time course on the articulate-language association in ASD
- Longitudinal data through school age
  - Persistence in brain-behavior relationship
  - Predictive power of microstructure at 2 years --> school age outcomes
- Need more data to strengthen this tool as a biomarker of later language or monitoring tool to measure effectiveness of language interventions
- Further parsing the HL-ASD group by language growth trajectory may reveal more subtle differences in the language-WM endophenotype

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Thank you!
Questions?

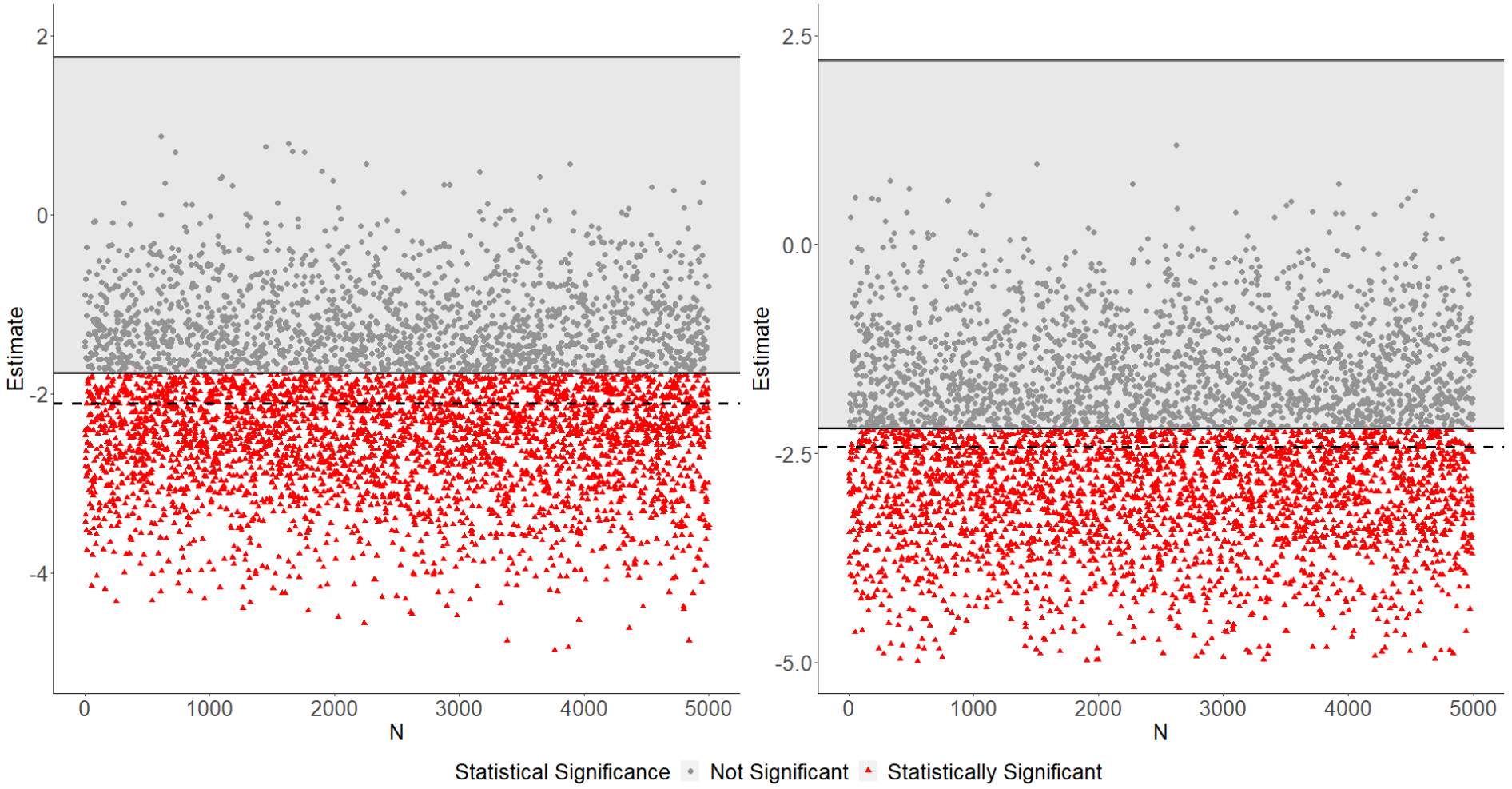
For questions: tyler_mcfayden@med.unc.edu

Supplementary Slides

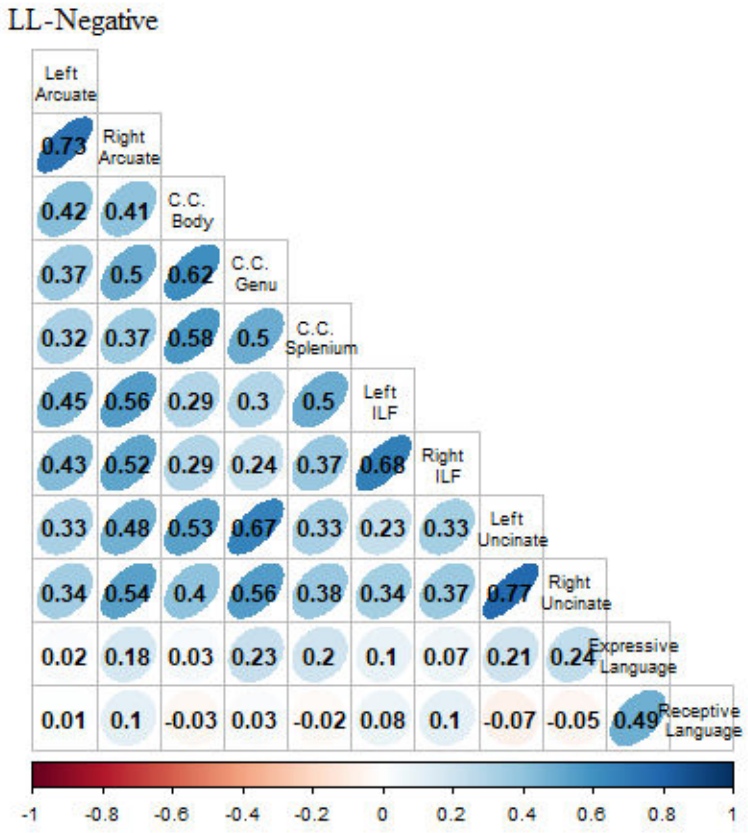
Participant characteristics

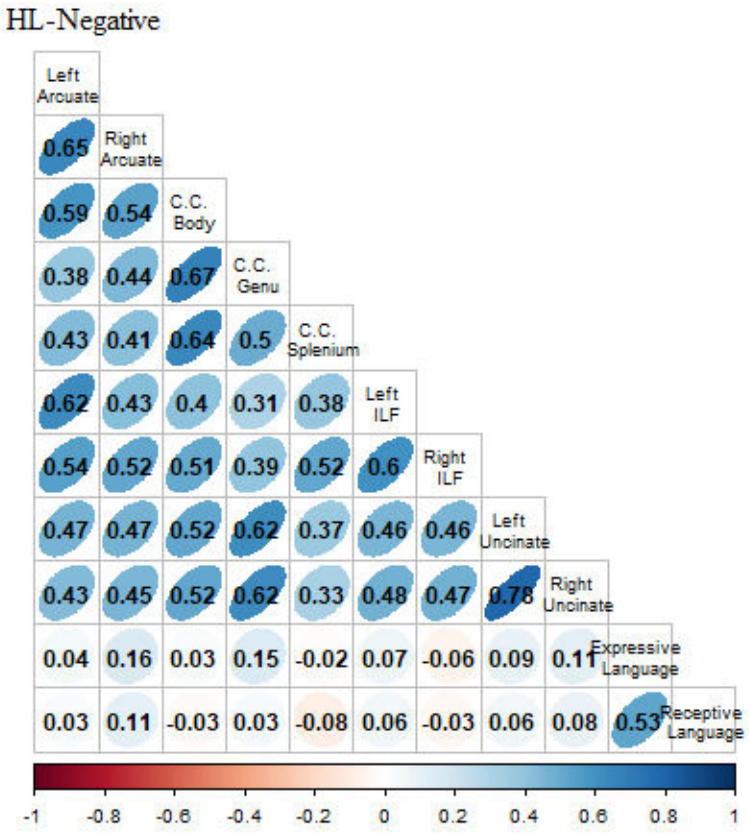
	HL-ASD (n = 70)	HL-Neg (n = 251)	LL-Neg (n = 140)
Female (%)	10 (14%)	116 (46%)	58 (41%)
Maternal Education (% College or higher)	64 (93%)	224 (90%)	133 (97%)
Site			
Philadelphia	17 (24%)	62 (25%)	27 (19%)
Seattle	17 (24%)	49 (20%)	37 (26%)
St. Louis	16 (23%)	77 (31%)	28 (20%)
UNC	20 (29%)	63 (25%)	48 (34%)
Race			
Asian or Pacific Islander	0 (0%)	4 (2%)	1 (1%)
Black/African-American	1 (1%)	4 (2%)	7 (5%)
More than one	10 (15%)	27 (10%)	19 (13%)
Unknown	0 (0%)	0 (0%)	1 (1%)
White	59 (84%)	216 (86%)	112 (80%)
ADOS RRB (24 Months)	6.46 (2.3)	2.97 (2.3)	2.17 (1.9)
ADOS SA (24 Months)	6.00 (1.9)	1.87 (1.1)	1.70 (1.0)
MSEL-EL Age Equivalent (6 Months)	5.47 (1.3)	5.52 (1.4)	6.06 (1.6)
MSEL-EL Age Equivalent (12 Months)	10.3 (3.0)	11.9 (2.8)	12.7 (2.8)
MSEL-EL Age Equivalent (24 Months)	18.9 (6.3)	23.9 (5.5)	25.8 (5.4)
MSEL-RL Age Equivalent (6 Months)	5.70 (1.6)	5.97 (1.7)	6.38 (1.6)
MSEL-RL Age Equivalent (12 Months)	9.84 (2.7)	11.2 (2.4)	12.3 (2.2)
MSEL-RL Age Equivalent (24 Months)	17.9 (7.7)	25.9 (4.4)	28.0 (4.4)

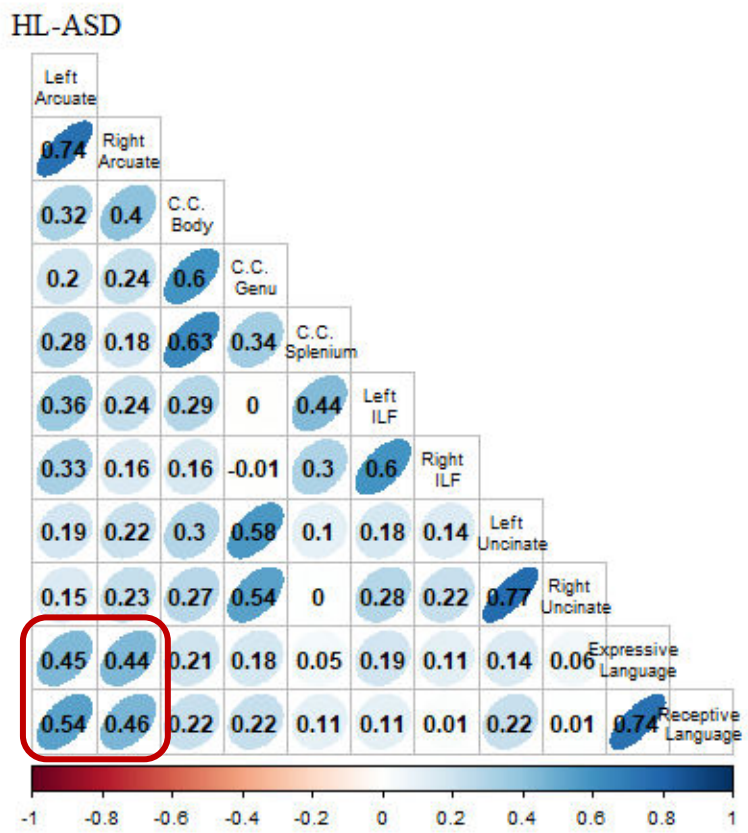
Type S and Type M Errors



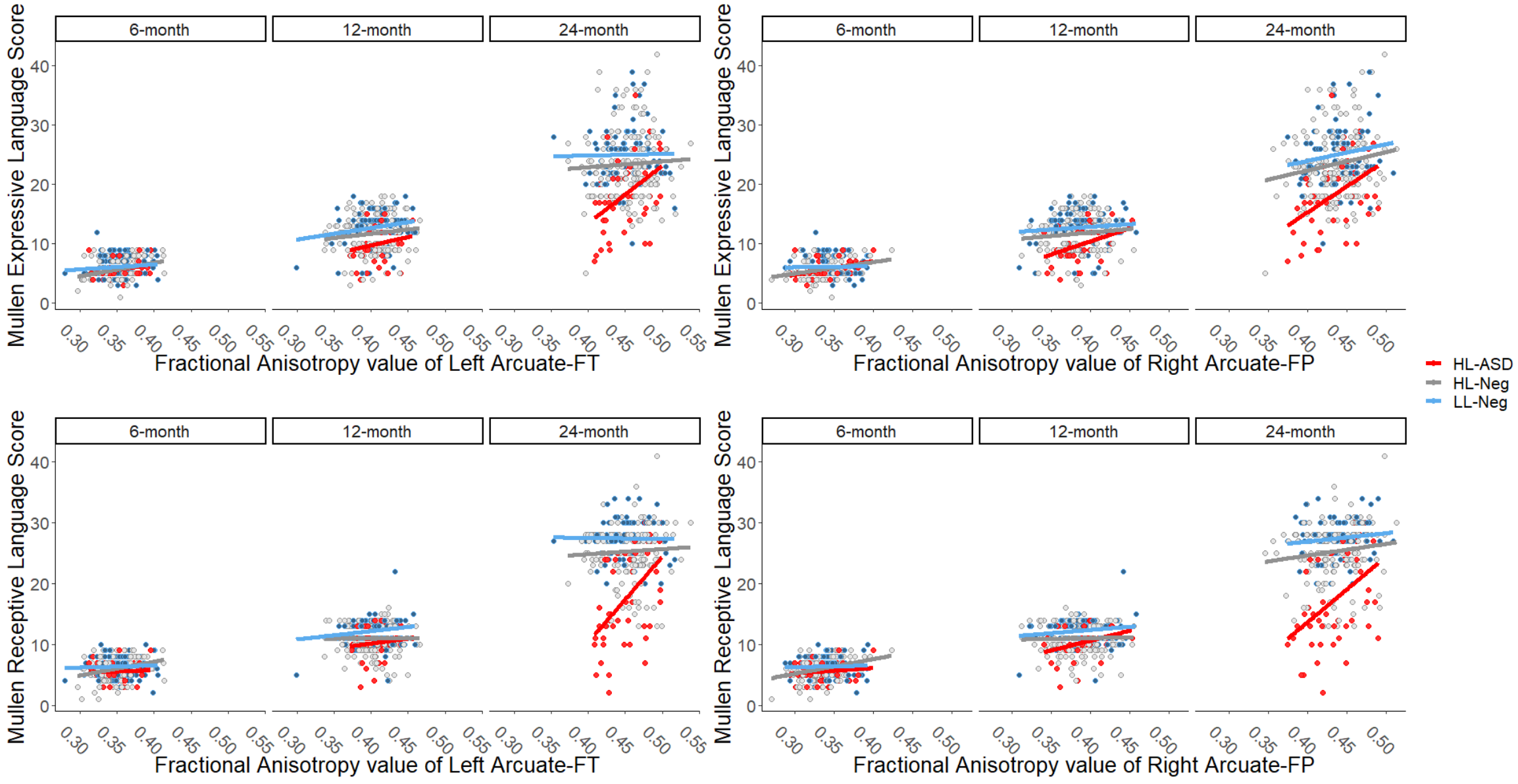
Arcuate and Language Relationship Unique to HL-ASD







Correlations between Expressive/Receptive Language and Microstructure Regions at 24 months


6-month
12-month
24-month
Mullen Expressive Language Score
Mullen Receptive Language Score
Fractional Anisotropy value of Left Arcuate-FT
Fractional Anisotropy value of Right Arcuate-FP
HL-ASD
HL-Neg
LL-Neg