White matter matters in the recovery of language in post-stroke aphasia

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Background

- Lesion size has been highlighted as a critical predictor of language outcome in persons with stroke-induced aphasia (PWA)[1-2]
- Lesion symptom-mapping studies have implicated specific gray matter (GM) structures in certain language skills (e.g., naming, lexical-semantics)[3-8]
- Due to structural disconnect, metrics of regional white matter (WM) integrity may be more powerful predictors of language skills in PWA than GM metrics alone[9-10]
- However, the potential compensation by remaining GM and WM left hemisphere (LH) structures *and* their right hemisphere (RH) homologues[11-12] has received little attention in the context of naming in patients with anomia

Research Questions (RQs)

RQ #1: To what extent does the integrity of core LH WM regions differ from RH homologues in PWA?
Hypothesis: Fractional anisotropy (FA): LH < RH; mean diffusivity (MD): LH > RH

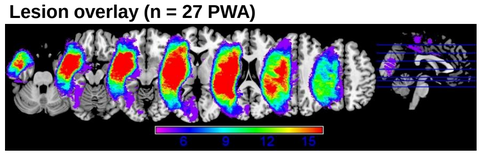
RQ #2a: What is the relationship between bilateral GM and WM integrity and (a) aphasia severity and (b) naming skills in PWA?
Hypothesis: All LH ROIs will predict aphasia severity whereas the strongest predictors of naming will be middle temporal and inferior frontal areas and their RH homologues[3-8]

RQ #2b: What type of LH model is best for predicting language?
Hypothesis: GM+WM model will better predict language than either GM only or WM only models[10]

Participants

- 27 PWA (17M, 24 right-handed, mean age = 62.3 ± 10.5 years, time post CVA onset = 55.0 ± 52.1 months)
- The Western Aphasia Battery-Revised[13] was used to index overall aphasia severity via the Aphasia Quotient (AQ)
- A 180-item non-standardized picture naming probe was administered to assess naming abilities
- PWA ranged in severity of aphasia and naming impairment as well as size and location of lesion

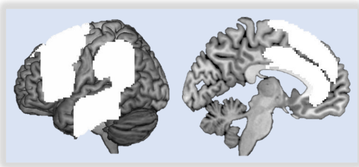
Lesion overlay (n = 27 PWA)



ID	Lesion Volume (cc)	WAB AQ	Naming Probe (%)
BU01	74508	87.2	58.3
BU02	205712	25.2	1.1
BU03	193278	52.0	17.6
BU04	92057	74.1	68.0
BU05	172344	30.8	6.1
BU06	324719	66.6	55.6
BU07	210628	48.0	14.1
BU08	79770	82.8	73.9
BU09	11279	95.2	59.1
BU10	68088	80.4	64.8
BU11	22680	92.1	33.2
BU12	210383	40.0	2.8
BU13	8097	92.7	60.9
BU14	59140	64.4	40.2
BU15	130489	87.2	56.1
BU16	321907	33.6	1.3
BU17	159060	74.3	52.2
BU18	154879	78.0	48.3
BU19	87744	28.9	7.4
BU20	257144	13.0	0.0
BU21	371222	11.7	0.4
BU22	97246	65.4	7.2
BU23	171038	45.2	5.2
BU24	235770	40.4	5.7
BU25	136854	37.5	2.2
BU26	89004	58.0	20.6
BU27	56449	84.3	45.9
AVG	148203	58.85	29.93
STDEV	97140	25.66	26.29

Methods: MRI Data Acquisition

- Images acquired on a 3T Siemens Trio Tim scanner with a 20-channel coil
- T1-weighted (TR/TE = 2300/2.91ms, slice thickness = 1mm, 176 sagittal slices), TR-FLAIR (TR/TE = 9000/90ms, slice thickness = 5mm, 35 slices, acceleration x2) and DTI (TR/TE = 900ms/92ms, slice thickness = 2mm, 70 interleaved slices, b = 1000 s/mm2) scans collected
- Eight regions of interest (ROIs, i.e., [ACC]; superior, middle, and inferior frontal gyri [SFG, MFG, IFG]; middle and inferior temporal gyri [MTG, ITG]; and supramarginal and angular gyri [SMG and AG]) were identified and masks were extracted from the Harvard-Oxford (H-O) cortl-maxprob-thr0, 1mm template



LH H-O masks pictured. RH masks also extracted

Methods: MR Data Processing

Cortical gray matter

T1-weighted images:
- Lesion masks (lesion = 0) & maps (lesion = 1) manually drawn for each patient in MRIcron
- Lesion masks & maps used in segmentation and normalization

GM integrity metrics:
- Lesioned LH ROIs generated for each patient
- Cortical integrity calculated by % spared tissue = (H-O ROI volume) – (normalized lesion volume) / (H-O ROI volume) in MarsBaR

Percentage (%) of spared cortical tissue

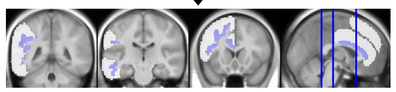
	ACC	SFG	MFG	IFG	MTG	ITG	SMG	AG
BU01	100.00	100.00	99.91	97.56	96.03	100.00	51.56	54.13
BU02	99.44	98.94	84.95	49.81	53.47	89.10	33.71	68.77
BU03	100.00	100.00	96.20	89.27	25.75	86.11	25.74	23.14
BU04	100.00	100.00	100.00	100.00	45.34	90.62	64.82	49.78
BU05	100.00	100.00	100.00	70.33	18.07	67.58	62.32	65.86
BU06	100.00	99.44	56.48	6.16	32.13	91.42	8.43	4.07
BU07	94.31	99.90	97.65	94.81	85.12	99.08	25.59	28.56
BU08	100.00	100.00	99.77	83.81	68.20	100.00	96.03	99.16
BU09	100.00	100.00	100.00	100.00	94.06	99.60	100.00	100.00
BU10	100.00	100.00	100.00	100.00	100.00	100.00	35.89	25.89
BU11	100.00	100.00	100.00	100.00	100.00	96.69	100.00	100.00
BU12	100.00	100.00	89.03	19.95	72.10	96.97	56.19	86.96
BU13	100.00	100.00	100.00	100.00	100.00	100.00	100.00	98.80
BU14	100.00	99.95	93.06	79.63	77.63	99.32	99.14	99.76
BU15	99.72	97.24	70.79	75.56	100.00	100.00	87.25	80.26
BU16	96.06	78.57	31.79	26.45	22.82	79.24	29.81	44.99
BU17	100.00	100.00	95.48	50.66	45.57	96.89	90.71	90.71
BU18	100.00	100.00	99.91	68.59	50.13	99.00	79.33	90.67
BU19	100.00	100.00	96.50	61.85	100.00	100.00	98.04	100.00
BU20	100.00	100.00	60.35	0.62	43.64	99.56	1.81	7.78
BU21	98.31	92.69	33.52	0.00	46.60	95.25	7.06	17.83
BU22	100.00	100.00	100.00	100.00	99.37	89.18	100.00	100.00
BU23	99.86	67.86	40.16	67.00	97.51	100.00	56.44	73.67
BU24	94.03	99.90	98.94	54.76	55.77	99.56	68.67	54.65
BU25	100.00	100.00	100.00	83.11	61.26	98.00	78.87	78.66
BU26	100.00	100.00	86.68	67.08	75.29	99.56	99.22	100.00
BU27	100.00	100.00	99.86	99.85	100.00	100.00	100.00	100.00
AVG	99.32	97.57	86.33	68.40	69.11	95.29	65.06	68.30

Subcortical white matter

DTI images*:
- Enantiomorphic replacement of LH lesion using intact RH tissue
- Modified T1 and lesion mask warped to MNI space
- Alignment of original T1 to diffusion scan
- Eddy current correction, rotation of bvectors, and EPI distortion correction
- Diffusion tensor calculated and scalar maps (FA, MD) generated in MNI space

*Advanced Diffusion Preprocessing Pipeline from the Northwestern University Neuroimaging Data Archive (NUNDA; http://niacal.northwestern.edu/nunda_pipelines/18)

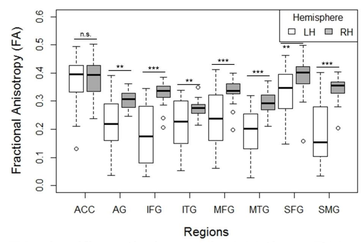
WM integrity metrics:
- Intersected the Harvard-Oxford (H-O) cortl-maxprob-thr0 and FMRIB58-FA 1mm templates
- Resampled intersected map to resolution of DTI outputs
- Broke overlay into H-O ROIs
- Overlaid ROIs onto patient's FA map
- Extracted mean FA and MD for bilateral ACC, AG, IFG, ITG, MFG, MTG, SFG, and SMG



Final cortical (white) and subcortical (blue-gray) masks

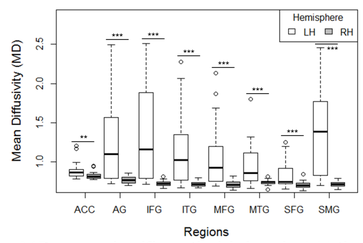
RQ #1 Results: WM Metrics by Hemisphere

FA by Hemisphere



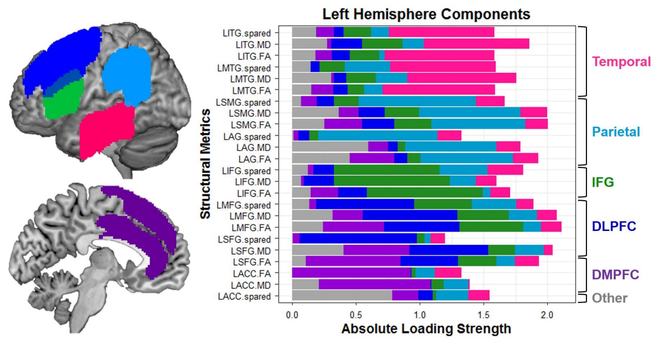
FA significantly lower in LH than RH ROIs ($F(1,52) = 10.15$, $p < .001$) except for ACC ($F(1,52) = 0.32$, $p = 0.58$)

MD by Hemisphere



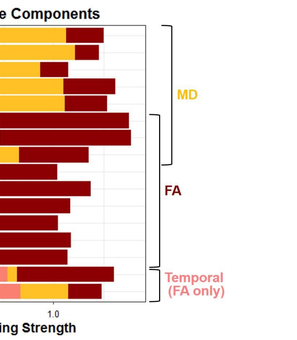
MD was significantly higher in LH than RH ROIs ($F(1,52) = 5.77$, $p < .001$)

RQ #2 Results: Language Predictions



- Six components resulted from the PCA including all LH metrics (i.e., FA, MD and %spared tissue)
- Metrics from certain adjacent regions loaded together

RQ #2 Results: Language Predictions



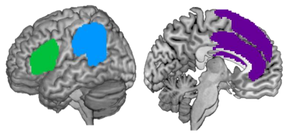
- RH metrics loaded together according to type, with all MD values and the majority of FA values loading together

Predictors of aphasia severity

- The final model included four LH components and RH MD values
- Only LH components were significant predictors of AQ

	Estimate	SE	t	p-value
Intercept	58.85	3.15	18.67	< .001
LH Parietal	9.06	3.25	2.79	0.011*
LH Temporal	8.74	3.21	2.72	0.13
LH IFG	14.56	3.32	4.38	< .001***
LH DMPFC	9.26	3.22	2.88	0.009**
RH MD	-5.95	3.37	-1.769	0.091

$F(5,21) = 8.56$, $p < 0.001$*, Multiple R-squared = 0.671**

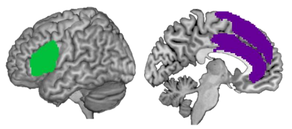


Predictors of naming abilities

- The final model included three LH components and RH MD values
- Only LH IFG and DMPFC significantly predicted naming

	Estimate	SE	t	p-value
Intercept	29.93	3.96	7.56	< .001
LH Temporal	6.93	4.04	1.72	0.1
LH IFG	11.44	4.17	2.74	0.012*
LH DMPFC	11.24	4.04	2.78	0.011*
RH MD	-7.65	4.12	-1.83	0.081

$F(4,22) = 5.11$, $p = 0.005$, Multiple R-squared = 0.482**



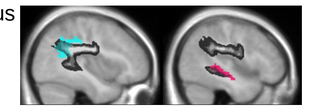
Comparing GM+WM to GM only & WM only models

Aphasia Severity
GM+WM model better than both GM only ($p = 0.20$) and WM only ($p = 0.004$) models

Naming Skills
GM+WM model better than GM only ($p = 0.04$) but no difference between WM only and GM+WM models

Conclusions

- Integrity metrics of LIFG and LH dorsomedial prefrontal regions were the strongest predictors of both aphasia severity and naming
  - LSMG and LAG—highly damaged regions in this sample—also predicted AQ
  - RH metrics (per PCA components) did not independently predict language skill
- For naming, the WM only and GM+WM models did not differ in predictive power
  - WM integrity of LIFG and LACC is likely most critical for word retrieval[10]
- WM adjacent to cortical ROIs (e.g., **LAG**, **LSMG**, and **LMTG**) aligns with established WM tracts like the arcuate fasciculus
- Next steps include determining the utility of regional versus entire tract integrity metrics in predicting language therapy outcomes



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