520.01

II6

Analyzing chronic stroke white matter lesions using a HARDI streamline database.

www.northerncalifornia.va.gov

T.J. Herron[1] & N. Dronkers[1,2,3] & A. U. Turken[1]

1 *U.S. Department of Veterans Affairs, VHA, Northern California Health Care System, Martinez Clinic, Martinez, CA, USA.* 2 *Neurology, University of California, Davis, CA, USA.* 3 *Neurolinguistics, National Research University Higher School of Economics, Moscow, Russian Federation.*

Neuroscience 2016

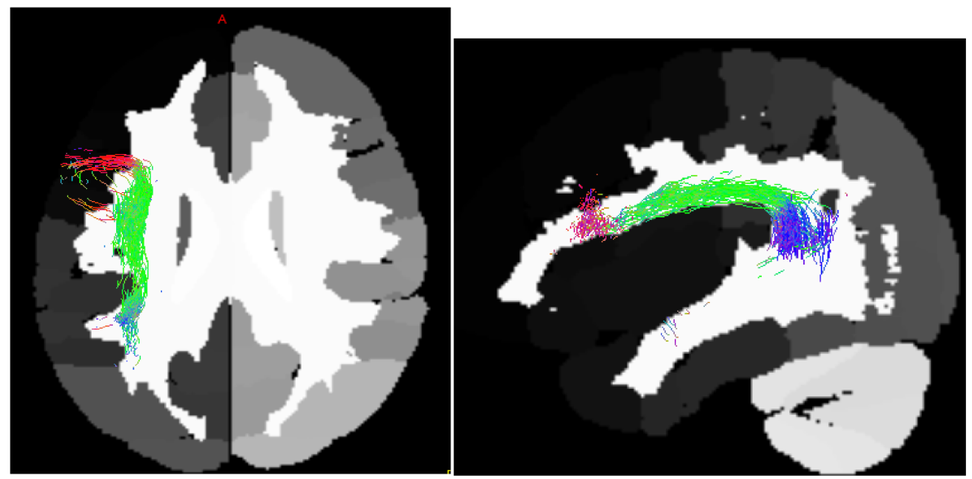
Abstract

We built a HARDI diffusion streamline atlas from 42 healthy, older controls in order to help identify likely connectivity deficits of chronic stroke patients for whom lesion masks are available specifying brain damage locations. We verified the accuracy of lesion mask-estimated connectivity deficits in 40 stroke patients by comparing atlas-estimated deficits to patients' actual HARDI streamline deficits (vs. the 42 age and sex matched controls). We then applied the streamline atlas to study a separate group of 191 left hemisphere chronic stroke subjects who suffered dysphasia and were imaged to generate hand-delineated lesion masks. We found that atlas-estimated white matter (WM) connectivity deficits contribute to explaining, along with regional gray matter (GM) damage and lesion size, behavioral speech and language deficits in the patient group.

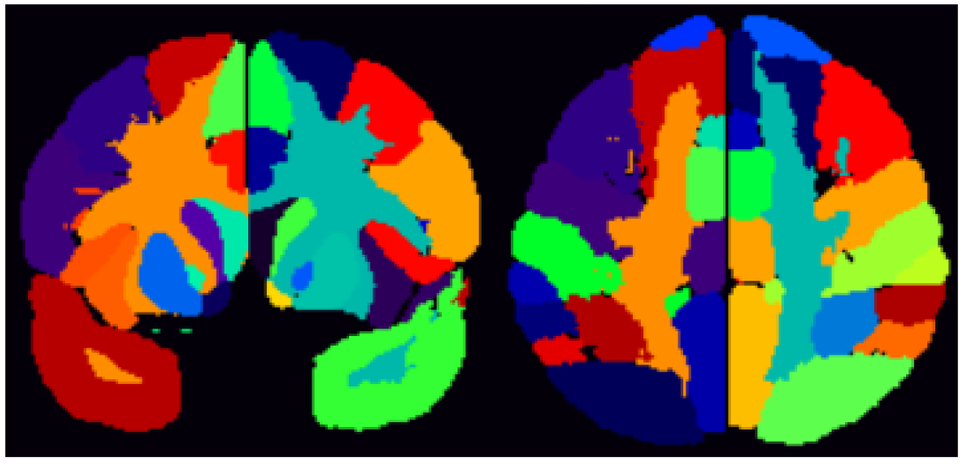
Streamline Atlas

HARDI images were processed using *mrtrix* to obtain 2.5M streamlines / control subject, seeded at random WM and GM locations. Streamlines were partitioned in native space using the Harvard-Oxford atlas specifying 48 cortical GM locations and 7 subcortical GM locations per hemisphere.

After further filtering and transformation, 13.9M streamlines traversing 0.4M possible MNI WM locations were produced and classified according to which pairs of the 110 GM ROIs they connect.



One control subject's HARDI streamlines from ROI F3o to T2p



Harvard-Oxford 110 parcel GM atlas

Table shows ANOVA results when verifying atlas connectivity estimates in our 40 patient stroke cohort: lesion mask-estimated connectivity deficits overlap well with deficits estimated directly from patient HARDI data.

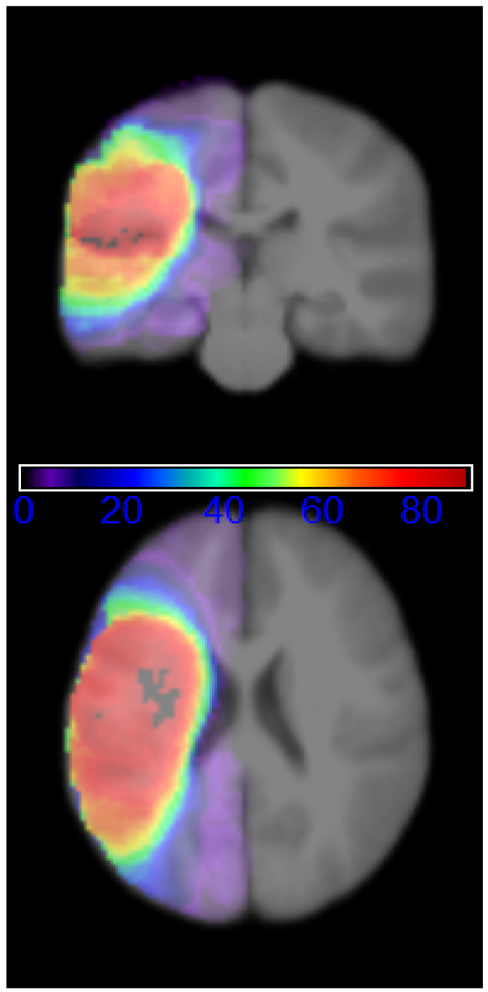
Mean matching agreement for estimated, binarized ROI-ROI connectivity deficits was 91.4% with significant factor modulations:
HARDI threshold (-1.6% at -2 ; $F_{3.117}$=28.7***)
Lobe (>+1% for limbic, occipital, and subcortical ROIs; $F_{5,195}$= 7.4*)
Hemisphere (+6.4% for Ipsi ; $F_{1.39}$=42.0***)
Mask threshold x Hemisphere (≤ -3 Mask threshold best for Contralateral connectivity ; $F_{3,117}$=21.2***)
Mask x HARDI thresholds (≤ -3 best for Mask threshold ; $F_{9,351}$=11.7**)
Lobe x Hemisphere (Temporal & Parietal lowest contralateral connectivity agreement ; $F_{5,195}$=11.6***)
Lobe x Lobe (small lobe intralobar matching best ; $F_{25,975}$=11.3***)

* p<0.01 ; ** p<0.001 ; ***p<0.0001

Neuroscience 2016

Application to Chronic Stroke Aphasia

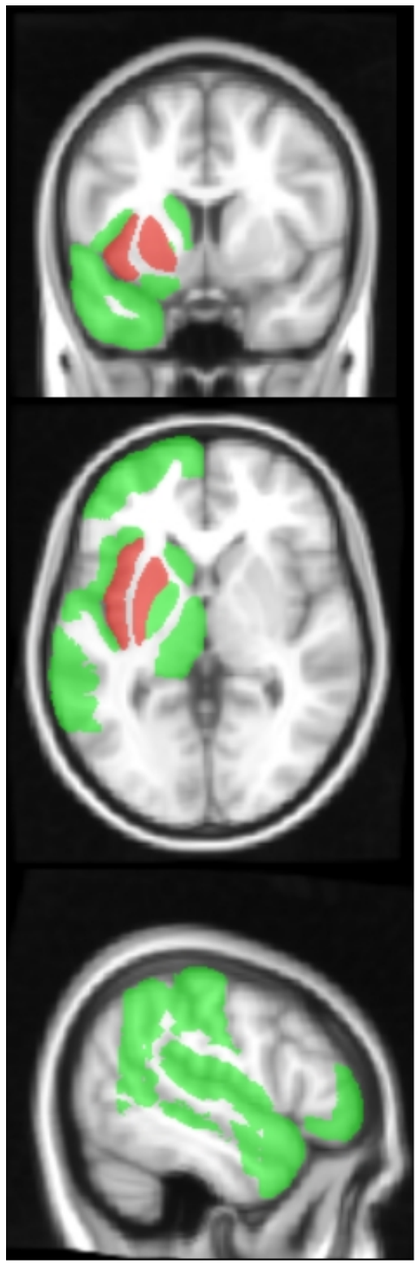
The streamline atlas is applied to a 191 patient chronic stroke cohort with lesion masks specifying left hemisphere lesions and with Western Aphasia Battery (WAB) scores [4].



WAB (Sub)Scores & Demographics	**Lesion Mask Variables + Demographics**
Aphasia Quotient	Total GM Lesion Size
Spontaneous Speech	Total WM Lesion Size
Repetition	Total WM Connectivity
Naming	Lobar GM Lesion Size
Comprehension	Lobar WM Lesion Size
	Lobar WM Lesion Connectivity
	Age, Sex, Education
	Time Past Event

When an increasing sequential linear regression is performed on the most important demographic and connectivity values, we found that global WM connectivity deficit scores improve the prediction of Aphasia Quotient (AQ) scores

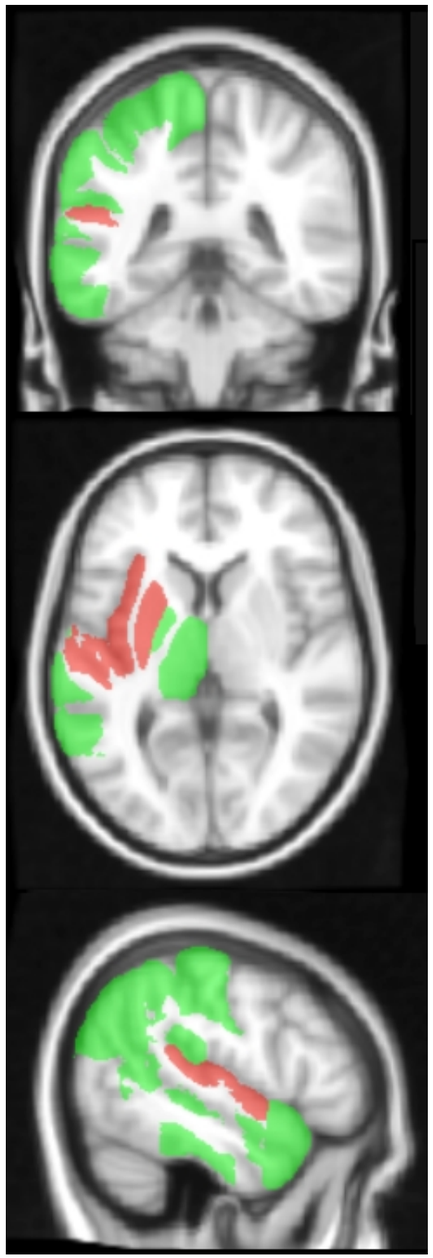
Variables Used	AQ Total Variance Explained	Comments
Age, Sex, Education, & log(Time Past Event)	**0.06**	**Demographics**
+GM Lesion Size	**0.50**	**From lesion mask + H-O MNI atlas**
+ WM Lesion Total Hemispheric Disconnection	**0.58**	**Using HARDI connectivity atlas, all values**
+ Temporal Lobe WM Hemispheric Disconnection	**0.63**	**Using HARDI connectivity atlas, temporal lobe values**



4 secondary Partial Least Square analyses were performed over each WAB subscore (using their component scores) vs. GM and WM lesion size plus all 55 Left hemisphere WM connectivity and GM damage values.

Spontaneous Speech PLS Result:
Green = WM Disconnection affects Spontaneous Speech ; Red = Both GM Damage and WM Disconnection affect Spontaneous Speech.

We found one major component ($Q^*=0.052, r^2=0.45$) in the Spontaneous Speech PLS: that GM ROI disconnectivity due to WM damage is more critical than GM ROI damage, as illustrated in the Figure. In addition, WM lesion size overall is the strongest factor.



Partial Least Square analysis performed over the Comprehension WAB subscore (components: Yes/No Questions, Auditory Word Recognition, Sequential Commands) vs. GM and WM lesion size plus all 55 Left hemisphere WM connectivity and GM damage values.

Comprehension PLS Result:
Green = WM Disconnection affects Comprehension ; Red = Both GM Damage and WM Disconnection affects Comprehension.

In the one major PLS component ($Q^*=0.073, r^2=0.37$) found associated with Comprehension scores, we see again that regional connectivity disruptions (along with WM and GM lesion sizes) factor more strongly than regional GM damage in the component's weights.

Neuroscience 2016

Discussion/Conclusion

We believe that this is the first study to attempt to verify the performance of a WM connectivity atlas - for application to stroke data and generated using diffusion data - by estimating diffusion connectivity of stroke patients using HARDI data and comparing that to the connectivity estimated using the atlas [2]. The use of all HARDI streamlines rather than expert delineated fiber bundles subsets [3] comes from our goal to capture all connectivity (including shorter/"U" fibers), not just connectivity due to named bundles. Current performance is encouraging – connectivity estimates appear to contribute to explaining post-stroke behavior - but more work is required to make sure that atlas connectivity matches that of patient HARDI connectivity as well as estimating how well HARDI connectivity matches true axon connectivity and it affected by ROI size and placement.

Thanks to Krista Schendel, Brain Curran (plus the whole lesion reconstruction team), and Xiaojian Kang for support.

[1] Tournier, J.D. et al, 2012 ; DOI: 10.1002/ima.22005 www.brain.org.au/software
[2] Kuceyeski, A. et al, 2015 ; DOI: 10.1002/hbm.22761 DOI: 10.1089/brain.2013.0147
[3] Thiebaut de Schotten M. et al 2014, DOI: 10.1093/cercor/bhs351 sourceforge.net/projects/tractotron
[4] Kertesz, Aphasia and Associated Disorders, Gruene&Strattion, 1979

Support was provided by VA Research Service CSR&D 1 I01 CX000586-01A1.
The opinions herein are those of the authors, not the U.S. Government or the Dept. of Veterans Affairs.

HARDI Streamline Atlas Details

HARDI DTI images: 64 isotropic gradient directions interspersed with 10 non-diffusion weighted (B0) images, high diffusion weighting (b=2000 s/mm^2). 65 axial slices (interleaved, no gap), 2 mm^3 isotropic voxels (240 mm FOV, 120x120 matrix). 42 healthy controls age (mean 61) and education (mean 14) matched to stroke cohort.

HARDI processing: *mrtrix* ver. 0.2.11 [1] 2.5M streamlines / subject sampled from segmented GM and WM locations, Model FOD of order 8.

HARDI normalization: Using SPM12, mean B0 images were coregistered to high-res subject T2 images which were in turn were normalized (default settings) to MNI space.

Database extraction: Harvard-Oxford (FSL) atlas (25% probability) GM and WM segmentations were used to select streamlines (cannot stray outside brain matter). A database streamline must also intersect exactly two different GM ROIs (of the 110 total).

Database filtering: 3D inverse discrete cosine parameterization of streamlines up to 20th order to reproduce fixed length (100 point) streamlines - easier to process and to use. Incident locations recorded in 2x2x2 mm MNI space in a 700MB file.

Neuroscience 2016

Streamline Atlas Verification Details

Patient's HARDI streamline deficit measure: The z-score, compared to 42 controls, of the logarithm$_{10}$ of the number of HARDI-estimated streamlines (+1) connecting 2 ROIs.

Database & Lesion Mask estimated connectivity deficit measure: The logarithm$_{10}$ of the fraction of remaining streamlines between two ROIs after removing all streamlines that intersect any part of the lesion mask damaged area in MNI space.

Estimator of Agreement of HARDI vs Database&Mask Connectivity Deficits: Use two independent thresholds (both between -5 and -2) to create binary deficit measures for each ROI. Then use the matching distance measure – fraction of matching deficits plus matching non-deficit ROI pairs vs. the number of total pairs – to indicate level of agreement of white matter connectivity deficit.

ANOVA: Fully crossed within subjects for factors Mask&Database deficit threshold [-2,-3,-4,-5] X HARDI deficit threshold [-2, -3, -4, -5] X ROI$_1$ Lobe [Frontal, Parietal, Temporal, Occipital , Limbic, Subcortical] X ROI$_2$ Lobe X Hemisphere [Ipsi, Contral.

ANOVA over 40 chronic (6+ mo post) ischemic stroke patients.

Neuroscience 2016

Atlas Application Details

Chronic Stroke Aphasia Database: 191 subjects: 43 female, age 61.5 (mean) ±10.8 (std dev) , education 14.5 y ± 2.9 , time past event 47 mo ± 51. Lesion masks hand delineated from CT or anatomical MRI scans by experienced personnel and checked by a neurologist. Mask translated into 2x2x2 mm MNI space

WAB Scores : AQ of 71.3 ± 28.3. AQ and all subscores transformed to be more unimodal using a Kumaraswamy distribution transformation, that also accentuates mild performance impairment.

Sequential Linear Regression: Start with demographics, then proceed to global damage measures (GM+WM), then to global connectivity, finally to regional damage and connectivity, keeping the previous level's variable explaining the most variance.

Partial Least Squares Analyses : Use subcomponents of Spontaneous Speech (Information Content and Fluency) as targets vs demographics, GM and WM lesion size, 55 left hemisphere ROI GM damage fractions, and 55 WM connectivity damage values. We found one significant (tenfold cross-validated Q* score > 0) PLS component with the displayed factor weights squared accounting for > 50% of total.

Neuroscience 2016