

On-line Supplemental Section

Figure 1 summarizes the injury process of ischemic stroke.

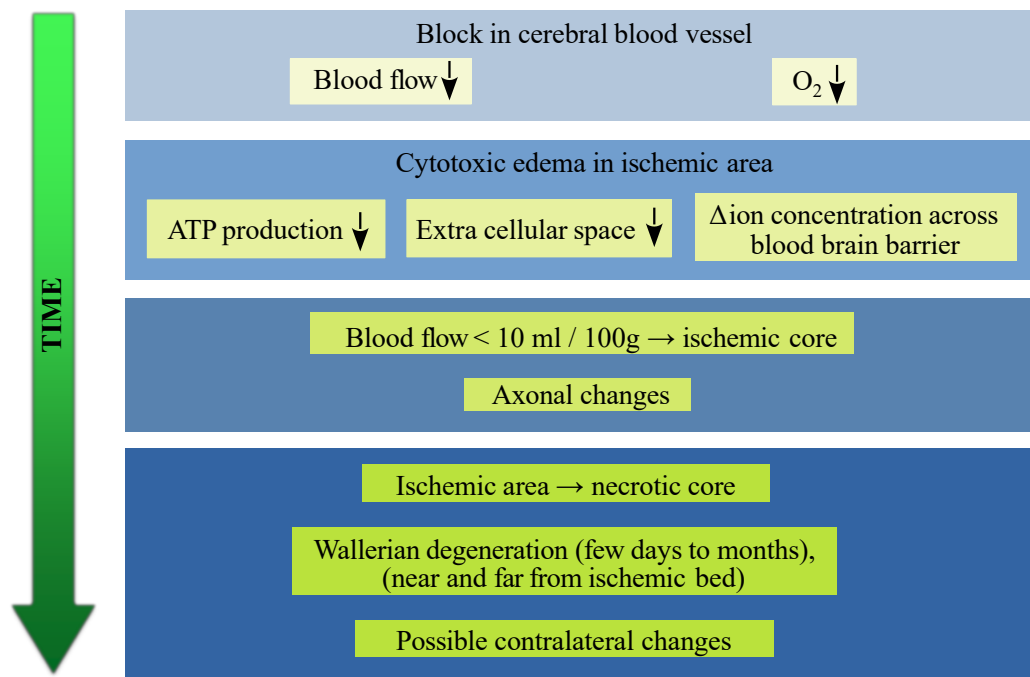


Figure 1: Approximate time course of ischemic stroke.

Figure 2(a) shows an example of a standard trace image and 13 parameter maps from a stroke subject - a 65 year old female imaged 1 week post-stroke with DSI⁹⁶, Fugl-Meyer upper extremity score=29. In Fig. 2(b), the histograms (normalized by number of voxels) are from manually drawn regions on the stroke and mirrored to the contralateral side and are shown to potentially better differentiate the distributions in the stroke and the matching contralateral regions, compared to the differences of the means in the regions.

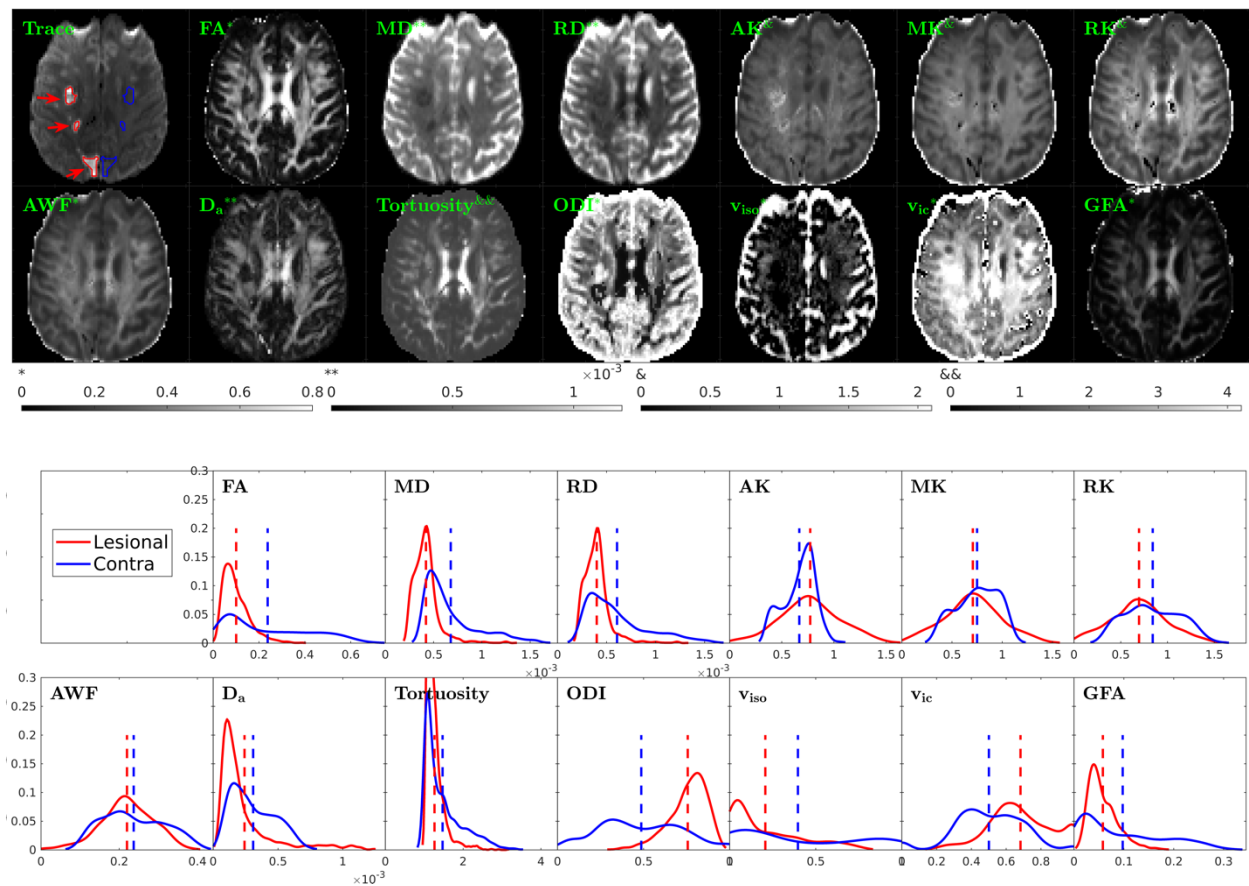


Figure 2: (a) Example of trace (upper left) and 13 parameter maps (see in glossary under DTI, DKI, WMTI, NODDI, and GFA). Stroke regions are marked shown with arrows on the diffusion trace image. The superscripts indicate which grayscale is used with each parameter. These encompass most but not all of the beyond DTI parameters reported in Tables 1-2. (b) Normalized histograms of the parameter distributions in 3D regions drawn in the stroke areas (red) and mirrored on the contralateral side (blue). Dashed lines show the mean values of the regions.

Table 1: Studies using DKI in Stroke Subjects

Paper	Number of subjects	Acquisition directions/b-values	TR/TE (msec)
	Time Points post-stroke		Number of slices
	Scanner	Spatial resolution	Scan time
	Analysis methods	Outcome measure	Results
Jensen et al. 2011¹⁰⁶	3	30/500, 30/1000, 30/1500,	1500/104
	13-26 hours	30/2000, 30/2500	9 slices
	Avanto 1.5T	2x2x5 mm ³	-
	ROIs, DTI, DKI	Percent change from contralesional	Greater changes in MK than MD. Large increases in AK, small in RK
Hui et al. 2012⁵	44	30/1000, 30/2000	5500/99
	6 hours to 2 weeks		40 slices
	Avanto 1.5T	3x3x3 mm ³	7 min
	Manual ROIs, DTI, DKI, and WMTI	Percent change from contralesional	MK showed more change than FA. WMTI (in FA>0.3) D _a changed the most
Zhang et al. 2017¹⁰⁷	77	25/1250, 25/2500	5000/98
	6 hours to 4 weeks, grouped into 4 intervals		-
	Discovery MR750 3T	1.875x1.875x4 mm ³	5 min 45 sec
	Manual ROIs, DKE	Changes in time post-stroke (unpaired groups)	AK and AD detected changes the best, PLIC most useful region
Chou et al. 2017¹⁰⁸	4	8/0, 30/1000, 30/2000,	6500/99
	3.3+-0.5 days	30/3000	25 slices
	GE 1.5T	3x3x3 mm ³	15 min
	ROIs, DKE	Used full 3 shell acquisition as reference	Using only subset of shells gave significant differences

Spampinato et al. 2017 ⁸²	17	10/0, 30/1000, 30/2000	5500/99
	1-4 days		40 slices
	Unspecified 1.5T	3x3x3 mm ³	7 min
	DKE, Fiber tracking to generate ROI of CST	FM at acute and 3 months	Rank correlation=.85 for MK, .78 for AK
Chen et al. 2018 ¹⁰⁹	21 with brainstem stroke	15/1000, 15/2000	6144/109
	Within 72 hours		48 slices
	Ingenia 3T	3mm slice thickness, unreported in-plane	9 min 54 sec
	ROIs at 4 locations. FA, MD, MK	change from contralesional, controls	MK, MD, FA all significantly different from contralesional
Yin et al. 2018 ¹¹⁰	37	20/1000, 20/2000	3300/95
	Two time points: 24 hours, 1 month		20 slices, SMS=2
	Trio 3T	1.6x1.6x5 mm ³ (1.25 mm gap)	2 min 10 sec
	Manual ROIs. FSL, DKE	T2-weighted lesion volumes at 1 month	MK lesion volume at 24 hours closest to outcome measure
Li et al. 2019 ⁸³	43	15/1000, 15/2000	4700/100
	10.1+-2 days		18 slices
	Discovery MR750, 3T	1.875x1.875x3 mm ³ (1.5mm gap)	4 min 12 sec
	Manual ROIs, GE functool	FM, Barthel index	rAK higher in those with ΔFM above recovery threshold
Zhu et al. 2019 ¹¹¹	156	15/1000, 15/2000 NEX=2	6000/162
	Not reported		
	Signa HDe 1.5T	2.5x1.9x5mm ³ , 1.5mm gap	6 min 18 sec
	Manual ROIs, GE functool	Percent change from contralesional	MK (and AK and RK) larger changes than ADC and FA

Yu et al. 2020⁸⁴	48	30/1000, 30/2000	5000/95
	3-7 days		Unreported, ~35 slices
	Discovery MR750, 3T	.94x.94x4 mm ³	Unreported, likely ~6min
	CST tract, voxelwise and slice-wise DKI	Percent change from contralesional. NIHSS motor portion at 3 months	Only AK correlated with NIHSS, r=0.3. FA or MD did not correlate.

Table 1: Studies using DKI in stroke subjects. A total of ten papers with n=450 total subjects. The number of b=0 scans is not included unless the number was clear from the manuscript. For acronyms see Glossary.

Table 2: Studies using GFA, SHORE, rate of kurtosis, or NODDI in stroke subjects

Paper	Number of subjects	Acquisition directions/b-values	TR/TE (msec)
	Time Points post-stroke		Number of slices
	Scanner	Spatial resolution	Scan time
	Analysis methods	Outcome measure	Results
Tang et al. 2010⁸⁸	7	203, max b=6000 (DSI)	9100/142
	90 days		45 slices
	Trio 3T	2.9x2.9x2.9 mm ³	Unreported, likely ~34min
	GFA. ROI or Tract-specific analysis	Lower extremity FM	GFA (only ipsilesional studied) correlates with FM, r~0.8 with ROI or tract-based
Granziera et al. 2012⁶	12	258, max b=8000 (DSI)	6600/138
	~1 week, again at 1 month, 6 months		34 slices
	Trio 3T	2.2x2.2x3 mm ³	26 min
	GFA between pairs of motor areas (regions mapped from MPRAGE)	NIHSS motor	Only contralesional studied. GFA+NIHSS+age predictive of 6 month NIHSS, adjusted r ² = .84
Lin et al. 2015¹¹²	10, same dataset as Granziera 2012	258, max b=8000 (DSI)	6600/138
	2 timepoints: 1 month, 6 months		34 slices
	Trio 3T	2.2x2.2x3 mm ³	26 min
	GFA between pairs of motor areas (regions mapped from MPRAGE)	NIHSS motor	Only contralesional studied. GFA distribution features depend on NIHSS, age, mRS
Brusini et al. 2016⁹¹	10, same dataset as Granziera 2012	258, max b=8000 (DSI)	6600/138
	~1 week, again at 1 month, 6 months		34 slices
	Trio 3T	2.2x2.2x3 mm ³	26 min

	6 SHORE indices	NIHSS motor	Only contralesional studied. All high correlation except RTAP. RTOP best (adjusted $r^2=.98$)
Galazzo et al. 2018²⁵	10, same dataset as Granziera 2012	258, max b=8000 (DSI)	6600/138
	~1 week, again at 1 month, 6 months		34 slices
	Trio 3T	2.2x2.2x3 mm ³	26 min
	SHORE indices as in Brusini et al. Also DTI (MD,FA)	NIHSS motor	MD and FA also predict NIHSS well. Most SHORE and DTI also changed in gray matter
Hodgson et al. 2019⁹⁶	9	203, max b=4000 (DSI)	3700/114
	3-12 days		51 slices
	Verio 3T	1.9x1.9x2.1 mm ³	13 min (SMS)
	NODDI, GFA, DTI in PLIC, stroke ROI and lesion load	FM at baseline and 38+-9 days post-stroke	ODI in the PLIC the best correlation with FM (optimism adjusted $r^2=0.83$)
Wang et al. 2019⁹⁷	71	25/1250, 25/2500	5000/98
	Single time point, groups of: 0-6 hours n=6, 6h-3days n=23, 3days-2 weeks, n=42		
	Discovery MR750 3T	1.875x1.875x4 mm ³	5 min 45 sec
	Stroke ROIs, DKE, DTI, DKI, NODDI	Unpaired changes in parameters at different times post-stroke	ODI changes the most over hours to 2 weeks times post-stroke (unpaired) – and ODI more sensitive than DTI or DKI

Mastropietro et al. 2019⁷	17	12/0, 20/700, 64/2000	16,900 ms/96 ms
	~2 weeks, 10 rescanned at ~8 months		64 slices
	Verio 3T	2x2x2 mm ³	96x16.9=27min
	DTI, DKI, NODDI in PLIC and CP	Change from contralesional	FA, AD, RD, KA, AK, and ODI significantly different in ipsi and contra.
Lampinen et al. 2021³⁵	5	12/0, 6/200, 6/500,	2000/105
	~2 days, rescanned at ~9 days and ~100 days	6/1000...6/4000, two diffusion times each	5 slices
	Achieva 3T	2x2x4 mm ³	12 min
	Rate of kurtosis k and MK, ADC and FA in manual ROIs	-	Diffusion time dependence k may predict chronic ADC.

Table 2: Studies using GFA, SHORE, rate of kurtosis, or NODDI in stroke subjects. A total of nine papers, with n=121 total stroke subjects. Note that four papers use the same ~10 subject dataset. Two of the studies also include DKI but are shown only in this table to reduce redundancy. The number of b=0 scans is not included unless the number was clear from the manuscript. For acronyms see Glossary.

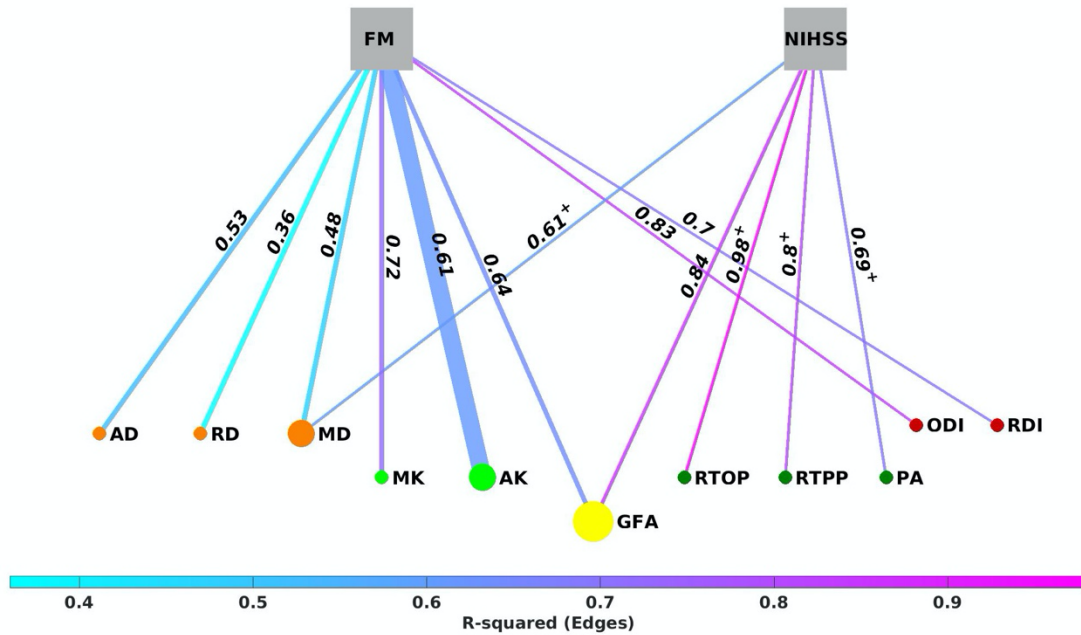


Figure 3: Summary of beyond DTI papers with outcomes (FM or NIHSS at ~1-3 months). The edge colors and labels are based on the 'best' R-squared value across papers for that pair. R-squared calculated from correlation where possible. A '+' sign indicates that other predictors (stroke size, age, etc) were a part of the joint model from which the R-squared is reported. We choose the 'best' vs. say, 'average' value across papers as some models may be multivariate or report p-values (no correlations) making it harder to quantitatively combine across papers. Edge thickness (scaled across edges) is based on the total number of subjects from all the papers contributing to that edge. In our case, only two edges (between FM and AK and between FM and GFA) have multiple contributing papers. Node sizes/colors: Scaled based on number of papers from the pool using that particular diffusion parameter. We have removed redundancy in this calculation that arises from papers using the same data set.

While the papers with outcomes have significant heterogeneity making a traditional meta-analysis not possible, Figure 3 highlights that beyond DTI diffusion parameters report mostly better ability to predict or have significant correlations with motor outcome measurements compared to DTI parameters. The beyond DTI edge colors versus the DTI edge colors are roughly at two ends of the colorbar range.

Note that not all beyond DTI papers study outcome associations - so, the number of papers (node sizes) and number of subjects (edge thickness) in the graph underestimate the general enthusiasm and promising findings across the larger pool of papers covered in Tables 1 and 2.

The general rules followed to construct the graph (Fig. 3) were as follows:

- Within each paper, find reported correlation values between a given pair of diffusion parameter and a clinical score.
- If multiple papers use this pair, then choose the results which are unique. For e.g., if the papers use the same data set, assign only one edge between the pair with the best R-Squared value for this edge across these papers (e.g., between NIHSS and GFA). However, if the papers are unique, then each paper's sample size adds to the edge thickness and the best R-Squared value across papers determines the edge color (e.g., between FM and GFA).
- Choosing 'best' r-squared value: In general, pick results with single-predictor models whenever possible. Multiple predictors in the model or multivariate analysis makes it harder to isolate the contribution of the exact diffusion parameter we are analyzing. The graph marks some edges with a '+' sign. These edges combine baseline measurements like stroke size, and age in the model and so the reported R-squared value of the edge is for the entire model and not the diffusion parameter alone.

Glossary

AD	Axial Diffusion. Computed from DTI - diffusion parallel to the primary eigenvector direction (the main fiber direction)
ADC	Apparent Diffusion Coefficient. The quantitative diffusion value in mm^2/s , termed “apparent” because of assumptions such as the distribution of diffusing spins is Gaussian. Note that when the diffusion value (ADC) is higher, the signal in diffusion-weighted images is lower.
AK	Axial Kurtosis. Non-Gaussian portion of diffusion signal in the direction parallel to the main fiber orientation
BCI	Brain Computer Interface. Could refer for example to a system with an EEG, processing, motor imagery, virtual reality, and functional electrical stimulation (FES)
Diffusion propagator	Also called 3D probability distribution function and ensemble average propagator (EAP). This fully characterizes the distribution of diffusion of water in a voxel, and can be used to derive other measures such as the ODF.
DKE	Diffusion Kurtosis Estimator. Open-source software for computing DKI parameters.
DKI	Diffusion Kurtosis Imaging. An extension to DTI to add a higher order term so that non-Gaussian non-linear processes can be modeled. Can generate mean kurtosis (MK), axial kurtosis (AK), radial kurtosis (RK), and other parameter sets such as WMTI

DTI	Diffusion Tensor Imaging. The acquisition of 6 or more diffusion weighted images and construction of a representative tensor at each location
DSI	Diffusion Spectrum Imaging. Acquisition with a large number of diffusion weightings (usually multiple b values and numerous directions) on a Cartesian grid to fill q-space
EAP	Ensemble Average Propagator. See diffusion propagator. (technically is an approximation of the average diffusion propagator, this depends on the narrow pulse condition)
fMRI	functional MRI. Method to detect blood flow changes with dynamic MRI, usually in the brain.
FA	Fractional Anisotropy, a measure of the directional diffusivity of water.
FM	Fugl-Meyer. Test of motor functions, FM upper extremity is 33 items each with values of 0,1,or 2. So the scale is 0-66. 66 is normal function. Named from Dr. Axel Fugl-Meyer, the first author of the survey.
FSL	FMRIB (Functional Magnetic Resonance Imaging of the Brain) Software Library. Widely used open-source tools for functional, structural, and diffusion MRI brain imaging datasets.
GFA	Generalized Fractional Anisotropy, measure of anisotropy from HARDI methods (std(ODF)/rms(ODF))

KA	Kurtosis Anisotropy. Also termed kurtosis fractional anisotropy (KFA) - similar to FA for the diffusion tensor, ranges 0-1 but is related to the directional variation of the non-Gaussian diffusion
mRS	Modified Rankin Scale. Ranges from 0-6. Standard scale for evaluating how well stroke patients can perform activities of daily living.
ND	Neurite Density. A parameter of the NODDI model that is related to how many neurites are in a voxel of region of interest. Note that in stroke areas, ND is not related to neurite density and is more of a restricted diffusion index (RDI)
NIHSS	National Institutes of Health stroke scale.
NODDI	Neurite Orientation Dispersion and Density Imaging. A model with intra-neurite (v_{ic} or ND or restricted diffusion index RDI), extra-neurite, and CSF (viso) compartments, and an ODI term.
ODF	Orientation Distribution Function. Representation of HARDI data. Can be created from the Funk-Radon Transform of single shell HARDI data, or by integrating 3D PDF from DSI
ODI	Orientation Dispersion Index. A parameter in the NODDI model that reflects how parallel nerve fibers are in a voxel, versus how dispersed in direction the fibers are.
q-space	Name given to diffusion-weighted space where the b value is the radius and the gradient weightings specify the direction. The 3D Fourier transform of q-space gives a 3D PDF, termed the diffusion propagator.

RD	Radial Diffusion. Computed from DTI - diffusion perpendicular to the primary eigenvector direction (the main fiber direction),
RDI	Restricted Diffusion Index. In the NODDI model, another term for neurite density ND or v_{ic} since in stroke the parameter may not reflect neurite density.
RTAP, RTPP	Return To the Axis Probability (RTAP) and the Return To the Plane Probability (RTPP) represent the integral of the EAP along the main diffusion direction and over the plane passing through the origin and perpendicular to the main diffusion direction, respectively.
SHORE	Simple Harmonic Oscillator Based Reconstruction and Estimation. A model based on Hermite functions for diffusion spectrum imaging data. Also extended to 3D SHORE and provides parameters RTAP, RTPP, and propagator anisotropy.
SMS	Simultaneous Multi-Slice. Also termed multi-band and hyperband. Method for exciting slices at the same time, typically with RF phase or slice gradient blips (CAIPIRINHA) to help separate the slices at reconstruction.
WMTI	White Matter Tract Integrity. A set of parameters that can be estimated from DKI data. The parameters include axonal diffusion (D_a), extracellular diffusion (parallel and perpendicular D_e), tortuosity, and axonal water fraction (AWF).

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