Diffusion Segmentation (DSEG) Provides a Whole-Brain Metric of Structural Decline in Cerebral Small Vessel Disease related to Change in Cognition over Three-Years

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Introduction

- Cerebral small vessel disease **(SVD)** is an age-related disease of the perforating arterioles that supply the white matter **(WM)** & deep grey matter **(GM)** & brain stem.
- **SVD** is characterised by lacunar infarcts & white matter hyperintensities **(WMH)** shown on **MRI** & is associated with a pattern of cognitive decline in which executive function **(EF)** & information processing speed **(IPS)** decline while memory is relatively preserved [1].
- Diffusion tensor imaging **(DTI)** measures the magnitude & directionality of water to characterise local brain microstructure. **DTI** parameters have shown stronger relationships with cognition in cross-sectional analysis than **WMH** burden & atrophy & were the only imaging metrics to show significant change over a 1-year follow-up [2].
- **(DSEG)** is a diffusion segmentation technique that produces a spectrum of 16 discrete segments describing microstructure of brain tissue [3] (Fig. 1-A). Percentage contribution **(PC)** can be calculated for each segment across the whole brain.
- By calculating the dot product of each **DSEG** spectrum in reference to the patient with the most severely atrophied brain (Fig. 1-B), we calculated an angle of difference ***(θ)***.
- Over a **3-year** interval we predict that **DSEG *θ*** will decrease as disease severity increases & that these changes will be related to a decline in cognition.

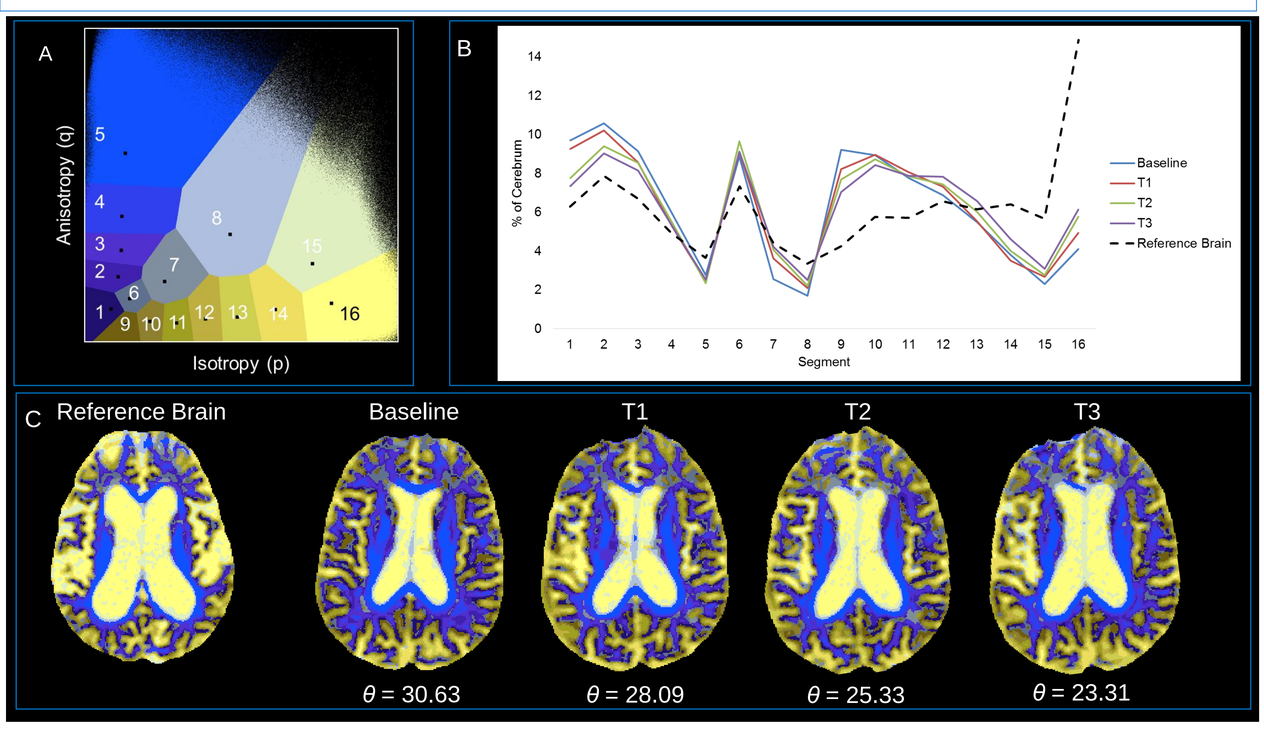


Figure1. (A) Showing DSEG segmentation of (p, q) space. (B) Spectra of example individual over 3-years. Reference brain spectra shown in black (C) DSEG visualisation of axial slices comparing the reference brain with slices of an individual at baseline & changing over 3-years.

Methods

- **Subjects:** Originally recruited for the St. George's Cognition & Neuroimaging in Stroke **(SCANS)** study. **99 patients** with clinical lacunar stroke & WMHs with longitudinal data.
- **Neuropsychological testing:** For each cognitive domain show, z-scores were derived for test listed & the modelled intercepts & regression gradients were averaged.
  - **Executive Function (EF):** Trail-making test (part B), single letter (FAS) verbal fluency, & the Wisconsin card sorting test.
  - **Information Processing Speed (IPS):** Digit symbol substitution, B-MIPB speed of information processing task, & the grooved pegboard task.
  - **Global Cognition (Global):** All of the above in addition to the WASI matrix reasoning & block design, Logical memory I & II and visual reproduction I & II from the WMS-III battery, & the Digit span.

•**Imaging:** DTI, FLAIR, T1 & T2*-weighted scans were acquired on a 1.5T Signa HDxt General Electric scanner.

•**Image Analysis:** WMH volume (**WMHV**), & atrophy were calculated using an automated segmentation technique [4] , **lacunes** & cerebral microbleeds (**CMBs**) were manually outlined on T1- & T2*-weighted images respectively, & **DTI** histogram parameters (Normalised Peak Height **(NPH)** and **median** for **MD** and **FA** were calculated using in house software [5].

•**Statistical Analysis:** Multivariate linear-mixed effects models were used to assess the relative impact of **DSEG *θ*** & other **MRI** markers on cognitive change. Only variables that were significantly related in univariate analysis were included.

DSEG Image Analysis

- DTIs were used to calculate ***p* (isotropic)** & ***q* (anisotropic)** metrics for each voxel in skull stripped images with the cerebrum removed.
- **DSEG** uses k-medians clustering to define **16 segments** in **(*p, q*)** space.
- Initial segments are defined by the quartiles of the ***p* & *q*** distributions.
- The median ***p* & *q*** values for each cluster are then calculated.
- Each image voxel is then iteratively reclassified to a segment based on the **Euclidean distance** between the voxel ***p* & *q*** values & the nearest segment median ***p* & *q***.
- This provides a unique segmentation of the (*p,q*) space based on the diffusion characteristics of the sample (Fig. 1-A).

Dot Product Calculations

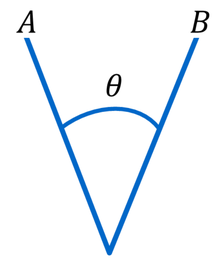
Dot Products (also known as vector inner products) allow computation of ***θ*** between two **vectors** (A & B) which are defined by the **DSEG** spectra as follows:

$$\theta = cos^{-1}\left(\frac{A \cdot B}{\|A\| \, \|B\|}\right),$$

where,

$$A = (a_1, a_2, \ldots, a_{16}),\ B = (b_1, b_2, \ldots, b_{16}),$$

$$\|A\| = \sqrt{(a_1^2 + a_2^2 + \ldots + a_{16}^2)} \ \&\ \|B\| = \sqrt{(b_1^2 + b_2^2 + \ldots + b_{16}^2)}.$$



Results

Table 1: Multivariate LME Models of Change in MRI Parameters Related to Change in Cognition

	EF		IPS		Global	
	Beta (S.E.)	***X²*, *p***	**Beta (S.E.)**	***X²*, *p***	**Beta (S.E.)**	***X²*, *p***
Baseline Age			**0.030 (0.007)**	**17.314, <0.001**		
Premorbid IQ	**0.046 (0.005)**	**102.529, <0.001**	**0.023 (0.004)**	**33.951, <0.001**	**0.035 (0.004)**	**83.401, <0.001**
DSEG *θ*	**0.047 (0.013)**	**12.697, <0.001**	**0.050 (0.012)**	**18.805, <0.001**	**0.035 (0.009)**	**14.766, <0.001**
MD NPH	-2.328 (40.480)	0.003, 0.954	2.373 (25.512)	0.009, 0.926	-13.135 (23.942)	0.301, 0.583
FA Median	-2.315 (3.265)	0.503, 0.478			1.796 (1.835)	0.958, 0.328
TCV	1.15e-006 (6.7e-007)	2.934, 0.087				
Lacunes	***-0.425 (0.183)***	***5.386, 0.020***	**-0.402 (0.161)**	**6.208, 0.013**		
CMBs	*-0.319 (0.155)*	*4.232, 0.040*	0.060 (0.142)	0.180, 0.672		

- **Table 1** shows the result of multivariate **LME** models predicting change in cognition using MRI parameters, baseline age & premorbid IQ.
- At univariate analysis **EF** was related to premorbid IQ & change in **DSEG *θ***, **MD NPH**, **MD Median**, **FA Median**, **TCV**, **lacunes** & **CMB**. When entered into a multivariate model, Premorbid IQ & change in **DSEG *θ*** & **new lacunes** were the only independent markers to remain in the model.
- **IPS** was related to premorbid IQ & age & change in **DSEG *θ***, **MD NPH**, **MD Median**, **FA NPH**, **FA Median**, **lacunes** & **CMB**. When entered into a multivariate model, Premorbid IQ & Age & change in **DSEG *θ*** & **new lacunes** were the only independent markers to remain in the model.
- Global cognition was related to **DSEG *θ***, **MD NPH**, **MD Median**, **FA Median**, **lacunes**, **CMB**, & premorbid IQ & age at a univariate level. When entered into a multivariate model, Premorbid IQ & **DSEG *θ*** were the only independent markers to remain in the model.
- Change in **DSEG *θ*** produced a highly stable marker of whole brain change related to cognitive change independent of all other brain markers.

Discussion

- We have found significant decline in whole brain microstructure & concomitant change in **EF, IPS and Global cognition** over a **3 year period**. This suggests that **DSEG** spectra can provide a biomarker of microstructural change that is related to cognitive decline in **SVD**.
- **DSEG *θ*** remained an independent marker of brain change in **SVD** when controlling for atrophy, **WM microstructural** changes described by **MD** and **FA** and **new lacunes** and **CMBs**. This suggests that it explains variance in change in cognition beyond that explained by these conventional markers of **SVD** damage.
- By describing the relative contribution of each discrete diffusion segment within a vector we capture **subtle interactions** between changes in healthy, damaged & atrophied tissue across the whole brain.
- Future Work will investigate the importance of individual **DSEG** segments in cognitive decline to provide predictive models for identification of individuals most at **risk of decline**.

References

[1] Roman et al., (2002). *Lancet Neurol*. 1: 426-436.[2] Nitkunan et al., (2008). *Stroke*. 39:1999-2005. [3] Jones et al., (2014). Neuro-Oncology. [4] Lambert et al., (2015). Neuorimage Clin 9: 194-205. [5] Lawrence et al., (2013). *Plos One, 8, e61014.*