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FULL PAPER

Repeatability of quantitative metrics derived from MR diffusion tractography in paediatric patients with epilepsy

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Objective: To quantify the test-retest repeatability of mean diffusivity (MD) and fractional anisotropy (FA) derived from diffusion tensor imaging (DTI) tractography in a cohort of paediatric patients with localization-related epilepsy.

Methods: 30 patients underwent 2 DTI acquisitions [repetition time/echo time (ms), 7000/90; flip, 90°; b-value, 1000 s mm⁻²; voxel (mm), 2 × 2 × 2]. Two observers used Diffusion Toolkit and TrackVis (www.trackvis.org) to segment and analyse the following tracts: corpus callosum, corticospinal tracts, arcuate fasciculi, inferior longitudinal fasciculi and inferior fronto-occipital fasciculi. Mean MD and mean FA were calculated for each tract. Each observer independently analysed one of the DTI data sets for every patient.

Results: Segmentation identified all tracts in all subjects, except the arcuate fasciculus. There was a highly consistent relationship between repeated observations of MD

($r = 0.993$; $p < 0.0001$) and FA ($r = 0.990$; $p < 0.0001$). For each tract, coefficients of variation ranged from 0.9% to 2.1% for MD and from 1.5% to 2.8% for FA. The 95% confidence limits (CLs) for change ranged from 2.8% to 6% for MD and from 4.3% to 8.6% for FA. For the arcuate fasciculus, Cohen's κ for agreement between the observers (identifiable vs not identifiable) was 1.0.

Conclusion: We quantified the repeatability of two commonly utilized scalar metrics derived from DTI tractography. For an individual patient, changes greater than the repeatability coefficient or 95% CLs for change are unlikely to be related to variability in their measurement.

Advances in knowledge: Reproducibility of these metrics will aid in the design of future studies and might one day be used to guide management in patients with epilepsy.

Epilepsy is a common neurological condition defined by recurrent unprovoked seizures that affects 1% of the population, including 1 in 200 children.^{1,2} Unlike in adults, developmental lesions predominate as the source of seizures in children; in particular, focal cortical dysplasia is the most common anatomical substrate for intractable epilepsy in the paediatric population.³ A high proportion of epilepsies occurring in the setting of cortical malformations are pharmacoresistant,⁴ highlighting the importance of alternative management strategies. In appropriately selected patients who fail medical management, surgical resection of the dysplastic cortex can be curative. In such cases, pre-operative identification and complete resection of the structural lesion are important prognostic factors.^{5,6} Decision making surrounding the pursuit of invasive alternatives is rarely straightforward, however, and in practice relies heavily on supplementary information provided by novel diagnostic techniques.

Although surgical management is an attractive option for many patients with focal seizures, medical therapy continues to be adopted as the "safe" strategy in a significant portion of this population. However, there is good evidence to suggest that ongoing seizures and treatment with anti-seizure medication might be associated with progressive alterations in white matter integrity.⁷⁻⁹ Furthermore, these same ongoing processes can contribute to progressive functional decline.^{10,11} As such, the ability to confidently identify progression of network alterations in an individual patient with epilepsy, whether on the basis of ongoing seizure activity, antiseizure medication or both, would be of great value to informed decision making surrounding potential surgical intervention.

With the advent of diffusion-weighted imaging (DWI), the microstructural properties of a tissue of interest can be non-invasively probed at a spatial scale that is otherwise unattainable using even the most advanced structural MR

techniques. Diffusion tensor imaging (DTI) is a variation on the theme of DWI, which quantifies water motion in three orthogonal dimensions and, therefore, is better able to capture the anisotropic tendencies of diffusion in highly organized tissues, such as cerebral white matter.¹² Numerous scalar metrics can be derived from the tensor; the most commonly referenced are mean diffusivity (MD) and fractional anisotropy (FA). MD provides a measure of overall incoherent motion within a voxel without regard for direction and reflects tissue organization at the cellular level.¹³ Increased MD is a common manifestation of white matter pathology of diverse aetiology.^{14–16} By contrast, FA provides a measure of the degree to which a single direction of water motion dominates overall diffusivity in a voxel. As such, FA has been shown to be a relatively robust measure of white matter integrity.^{17–21} Diffusion tractography is an extension of DTI in which the directional tendencies of water diffusion are used to create three-dimensional representations of white matter tracts based on their structural coherence.^{22,23} In many instances, the functional role of the constructed pathways is at least in part known, which enables assessment of brain parenchymal abnormalities in terms of functional systems.^{16,24}

DTI and diffusion tractography already occupy a prominent place in epilepsy research, and they are increasingly used to guide clinical management of epilepsy patients.^{7,25–30} Although preliminary results are promising, a thorough understanding of the test–retest reproducibility of metrics derived from DTI will be crucial to the widespread application of this technique. Such knowledge would inform the design of both cross-sectional and longitudinal studies, including appropriate sample size selection. Furthermore, the clinical utility of such quantitative techniques will be predicated on an understanding of their intrinsic variability at the level of the individual. In particular, an understanding of what represents true difference at the individual level will be required to ascribe significance to changes in these metrics that occur in an individual patient. To date, however, the reproducibility of quantitative metrics derived from tractography has not been widely studied and, in particular, there are very few data from either the paediatric or epilepsy populations.³¹ The goal of this study, therefore, was to measure the repeatability of MD and FA derived from DTI tractography in a cohort of paediatric patients with localization-related epilepsy.

METHODS AND MATERIALS

This Health Insurance Portability and Accountability Act (HIPAA)-compliant study was approved by the local institutional review board. Patients were identified retrospectively from an existing database of paediatric patients undergoing clinical evaluation as part of the institutional multidisciplinary epilepsy work group. The following inclusion criteria were applied: paediatric age group (≤ 18 years); MRI of the brain performed at 3 T; and two separate but identical DTI sequences performed in the same imaging session. Although it is not standard practice to perform duplicate sequences during a single examination, two technically sound acquisitions of the same DTI sequence are occasionally performed, for example, as a result of requests for tractography. To clarify, a duplicate diffusion sequence performed to ameliorate technical deficiencies in the initial acquisition would not be considered to meet the inclusion

criteria in this study. Refinements to the above-defined population were based on the following exclusion criteria: motion or other degradation to image quality; and clinical seizure during the imaging examination.

MRI technique

All imaging was performed on a single 3 T magnet (Siemens Tim Trio; Siemens Healthcare, Erlangen, Germany). The following sequences were obtained: sagittal magnetic preparation rapid acquisition gradient echo [repetition time (TR)/echo time (TE), 2530/3.39 ms; acquisition, 1; flip, 7°; inversion time, 1100 ms; acceleration, 2; and voxel (mm), $1 \times 1 \times 1$]; axial fast spin echo (FSE) T_2 weighted [TR/TE, 11,730/89 ms; acquisitions, 2; flip, 120°; acceleration, 2; and voxel (mm), $0.6 \times 0.4 \times 2.5$]; axial fluid attenuation inversion recovery [TR/TE, 9000/137 ms; acquisition, 1; flip, 150°; field of view, 22 cm; and voxel (mm), $0.7 \times 0.7 \times 4$]; and axial single-shot echo planar imaging DTI [TR/TE, 7000/90 ms; flip, 90°; acquisition, 1; voxel (mm), $2 \times 2 \times 2$]. For DTI, 35 image sets were acquired, 5 without diffusion weighting (b_0) and 30 with non-collinear diffusion-weighting gradients (b -value, 1000 s mm^{-2}). All images were visually inspected for artefacts, including subject motion.

Image processing and analysis

Maps of MD and FA were created using Diffusion Toolkit (www.trackvis.org). For each voxel, a tensor matrix was derived. After diagonalization of the matrix, eigenvalues were obtained, and MD and FA were quantified for each pixel according to standard equations.³² Diffusion Toolkit was used for deterministic tract reconstruction using a fiber association by continuous tracking algorithm (35° angular threshold). A DWI mask was used to remove cerebrospinal fluid, a process that has been shown to effectively prevent spurious tract reconstruction.¹⁶ Trackvis was then used for segmentation and analysis of the following major commissural, projection and intrahemispheric association pathways: corpus callosum; bilateral corticospinal tracts; bilateral arcuate fasciculi; bilateral inferior longitudinal fasciculi; and bilateral inferior fronto-occipital fasciculi. Regions of interest for tract segmentation were placed manually on the colour FA maps, which were cross referenced with the b_0 images according to previously described methods.³³ Mean MD and mean FA were then calculated for each identifiable tract.

Two observers experienced in tractography performed the tract reconstruction, segmentation and analysis. Each of the two observers evaluated one DTI data set for every patient—the first performed diffusion data set in half the cohort and the second acquisition in the other half, distributed at random. The two observers worked completely independently and were blinded to the results of the other observer. In summary, for every tract in every patient, the above analysis resulted in two estimates of each metric (one from each observer). It was these two estimates that were compared for the purposes of repeatability. This study design, therefore, does not simply reflect the variation between identical DTI acquisitions or that between observers but rather the aggregate of the two. This design was adopted to most closely reflect the expected circumstances when such analyses are incorporated into clinical workflow (follow-up examinations, in

most practices, would be very likely to be analysed and interpreted by a different neuroradiologist).

Statistics

Statistical testing was performed using SAS® software v. 9.2 (SAS Institute Inc., Cary, NC). The Wilcoxon signed-rank test (α , 0.05) was used to assess potential systematic differences between estimates of MD and FA from the two observers. Mean differences between estimates from the two observers were then compared for the following two subgroups, again using the Wilcoxon signed-rank test (α , 0.05): all tracts from structurally normal brains *vs* all tracts from brains with cerebral malformations; and all left hemispheric tracts *vs* all right hemispheric tracts. A potential relationship of repeatability with age was assessed by linear regression. Assuming no significant differences in repeatability between these subgroups, repeated measures of diffusion metrics were considered as a whole for the remaining analyses.

For each metric, we calculated the following: within subject standard deviation; mean coefficient of variation (CoV); root mean square (RMS) CoV; and Pearson's correlation coefficient. To estimate the magnitude of change that would be clinically detectable in a single individual, RMS CoV was used to calculate the 95% confidence limits (CLs) for detection of change.³⁴ A repeatability coefficient was also calculated as described by Bland and Altman.³⁵ For an individual patient, changes greater than the repeatability coefficient or 95% CLs for change are unlikely to be related to intramethod variability in the measurement of MD and FA. The mean CoV, repeatability coefficient, correlation coefficient and 95% CLs for change were also quantified for each white matter pathway (e.g. corticospinal tracts in all patients). In addition, the minimum sample sizes required to detect 1%, 2% and 5% changes in mean MD and mean FA were calculated for each tract (power, 0.9; α , 0.05). Kruskal–Wallis one-way analysis of variance was used to assess the possibility that repeatability might vary across different tracts (α , 0.05). Finally, for any white matter pathway not identified in all patients, Cohen's κ coefficient was calculated to assess agreement between the readers with respect to its absence/presence.

RESULTS

Patients

Imaging was performed from January 2009 to August 2011. The final study group comprised of 30 patients (age range, 1–18 years; median, 8 years). Of this cohort, 10 patients had structurally normal brains and 20 were diagnosed with cerebral malformations, including polymicrogyria ($n = 9$), focal cortical dysplasia ($n = 7$) and tuberous sclerosis ($n = 4$). Tract reconstruction and analysis identified all expected tracts in all subjects, with the exception of the arcuate fasciculus, which was not identifiable in the left hemisphere in five subjects, in the right hemisphere in four subjects and bilaterally in five subjects.

Repeatability

Repeatability across the data set was generally consistent. Specifically, the mean difference between observations for tracts segmented from structurally normal brains did not differ from those segmented from brains with cerebral malformations (MD,

$p = 0.74$; FA, $p = 0.82$). Similarly, no difference was detected in the mean difference between observations of left- *vs* right-sided tracts (MD, $p = 0.85$; FA, $p = 0.79$). Finally, no relationship between age and repeatability was detected for either MD ($p = 0.93$) or FA ($p = 0.89$). Hence, these groups were considered in aggregate for the remaining analyses.

No significant difference between observations from the two users was identified for either MD ($p = 0.78$) or FA ($p = 0.89$). Graphical representation of mean MD and mean FA is presented as described by Bland and Altman³⁵ in Figure 1. Differences between replicates were demonstrably independent of the mean. Furthermore, correlation analysis demonstrated a highly consistent relationship between observations of both mean MD ($r = 0.993$; $p < 0.0001$) and mean FA ($r = 0.990$; $p < 0.0001$). Test–retest estimates of the reproducibility of mean MD and mean FA are presented in Table 1. Repeatability was generally consistent across the different tracts for both MD ($p = 0.78$) and FA ($p = 0.52$), although a small range was observed (Table 2). The minimum sample sizes required to detect 1%, 2% and 5% changes in mean MD and mean FA are presented in Table 3. For the arcuate fasciculus, Cohen's κ coefficient for agreement between the readers (identifiable *vs* not identifiable) was 1.0 [95% confidence interval (1.0, 1.0)].

DISCUSSION

Intermeasurement variation in MRI reflects numerous factors, including scanner hardware, acquisition parameters and biological features related to the patient. There is also potential variability related to image processing, particularly when regions of interest are defined, at least in part, in a subjective manner. In our study, two users independently defined tract-based volumes of interest based on separate diffusion data sets acquired from the same patient in the same imaging session. Our findings indicate that, when performed on the same 3T scanner, there is good repeatability of mean MD and mean FA within major commissural, projection and intrahemispheric association pathways as defined by DTI tractography. Furthermore, the repeatability coefficients and 95% CL for detection of change reported here will allow for significance to be attached to changes in these metrics that occur in individual patients. Interval changes greater in absolute magnitude than the repeatability coefficient or in fractional magnitude than the 95% CL for change are unlikely to be related to intramethod variability in the measurement of MD and FA. It is important to note that our findings do not suggest that changes of lesser magnitude are without clinical significance; only that such change will not be reliably detected within an individual patient using this technique.

We have also provided an estimate of the minimum sample sizes that would be required to reliably detect relatively small changes in mean MD and mean FA. Power analyses are a critical step in the design of studies that aim to detect differences between groups or within the same group over time. In general terms, relatively small changes in MD or FA should be detectable with sample sizes commonly found in the neuroimaging literature. It is important to note, however, that the standard deviation of true changes within a given population, which will likely vary with the population of interest and study methodology, will

Figure 1. Bland-Altman repeatability analysis of (a) mean diffusivity (MD) and (b) fractional anisotropy (FA). Thick black horizontal lines denote the repeatability coefficient and bound the 95% confidence interval for change. Δ FA, difference between observations of FA recorded by the two observers; Δ MD, difference between observations of MD recorded by the two observers.

potentially reduce the minimal detectable differences in a given metric for a given sample size.

Finally, as exemplified by results from the arcuate fasciculus, a binary decision regarding whether a given tract is identified in a given patient was highly reproducible between the two observers. It is important to note the histopathological significance of failure to identify a tract at tractography is yet to be established. Formation of association pathways involves numerous developmental processes that act in a co-ordinated fashion to establish mature patterns of cerebral connectivity. These include,

but are not limited to, differentiation and maturation of pyramidal cells in cortical layer three, axonal genesis and guidance to the subplate, synapse formation and establishment of connectivity with the developing cortical plate, and selection (or pruning) of connections.³⁶ Failures at any of these steps might be expected to potentially result in an abnormal, or even unidentifiable, tract. Furthermore, in addition to absence of a tract in some absolute sense, failure to detect a white matter pathway with DTI could also reflect marked disorganization of white matter structure, resulting in a profound loss of tissue coherence. Regardless of the histology underlying such a finding, preliminary work has

Table 1. Repeatability of mean diffusivity (MD) and fractional anisotropy (FA) derived from diffusion tensor imaging tractography

Statistic	MD ($\text{mm}^2 \text{ s}^{-1}$)	FA
Mean	0.8970×10^{-3}	0.4900
Mean difference	0.0027×10^{-3}	0.0021
WSD	0.0130×10^{-3}	0.0104
CoV (%)	1.500	2.1000
RMS CoV (%)	1.500	2.4000
Correlation coefficient	0.993 ^a	0.9900 ^a
Repeatability coefficient	0.0370×10^{-3}	0.0290
95% confidence limits for change (%)	4.100	6.5000

CoV, mean coefficient of variation; RMS, root mean square; WSD, within subject standard deviation.

^a $p < 0.0001$.

suggested that absence of the arcuate fasciculus might have potential value as a biomarker of language delay in children.³⁷ The reliability of this assessment reported here lends credence to the idea that such a finding might indeed have potential clinical utility in the paediatric population.

To our knowledge, these data represent the first description of the repeatability of quantitative metrics derived from DTI tractography in patients with localization-related epilepsy. Interestingly, our results are generally comparable with those reported in tract-based studies of healthy adults at both 1.5^{38,39} and 3 T.^{40–44} Many of these studies have found MD to be generally more repeatable than FA.^{31,42,45} Although the difference is not statistically significant, the observed range in repeatability across different tracts is also consistent with previous reports.^{38,43,44} Although data from the paediatric population are extremely sparse, our results are also inline with a reproducibility study³¹ using a manual region of interest, rather than tractography, methodology in healthy children at 1.5 T. Similarly, reports are rare on the repeatability of DTI in cerebral pathology. One study of adult patients with high-grade brain tumours reported mean MD and mean FA to be less repeatable than in our study population.⁴⁶ This discrepancy could reflect the semi-manual, rather than tractography-defined, placement of regions of interest, a practice that has been reported to potentially result in greater variability.⁴⁷ Direct comparison to the study's results is difficult, however, owing to numerous

other methodological differences (including field strength, number of diffusion gradients and scan timing). As such, it remains to be determined whether the repeatability of these metrics will vary with the specific pathology of interest. It is worth noting that we found similar differences between observations for both structurally normal and abnormal brains. This finding raises the possibility that tractography-defined regions of interest might in fact be robust across a variety of cerebral conditions, a hypothesis that would be worthy of testing in future studies. The reproducibility of tractography with respect to its characterization of a given white matter pathway as present or absent has not, to our knowledge, been previously studied.

This study has several limitations. First, this is a study of a highly selected cohort of patients with localization-related epilepsy. As alluded to above, extrapolation of these results to patients with other types of central nervous system pathology might not be valid. Second, all imaging was performed on the same MR scanner with the same phased array coil. Further study regarding the reproducibility of these metrics across a wider variety of MR hardware would be of great practical value, especially in light of evidence that test–retest variation increases when performed on different types of magnet.^{43,45,48,49} Third, all diffusion data were acquired according to the same DTI pulse sequence. Recent work has suggested the potential for seemingly minor alterations in data acquisition, in particular the *b*-value and number of

Table 2. Repeatability of mean diffusivity (MD) and fractional anisotropy (FA) from individual white matter pathways

Tract	MD				FA			
	CoV (%)	CC	RC ($10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	95% CL	CoV (%)	CC	RC	95% CL
Callosum	1.4	0.994	0.036	3.9	1.6	0.999	0.024	4.6
Arcuate	1.1	0.998	0.024	2.8	1.5	0.994	0.019	4.3
CSP	2.1	0.973	0.049	6.0	1.9	0.986	0.032	6.5
IFOF	0.9	0.996	0.026	2.8	2.5	0.985	0.033	6.8
ILF	1.6	0.991	0.043	4.4	2.8	0.985	0.037	8.6

CC, correlation coefficient; CL, confidence limits for change; CoV, mean coefficient of variation; CSP, corticospinal tract; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; RC, repeatability coefficient.

Table 3. Minimum sample sizes required to detect 1%, 2% and 5% changes in mean diffusivity (MD) and fractional anisotropy (FA)

Tract	MD			FA		
	1%	2%	5%	1%	2%	5%
Callosum	49	15	5	56	17	5
Arcuate	40	12	4	52	15	5
CSP	86	23	7	76	21	6
IFOF	43	13	4	93	24	7
ILF	53	17	5	102	28	9

CSP, corticospinal tract; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus.

diffusion gradient directions, to impact the measurement of metrics derived from DTI.^{44,47} Hence, equivalence should be tested, rather than assumed, when designing future studies that will incorporate multiple pulse sequences. Fourth, this study addressed the repeatability of diffusion metrics based on the tract segmentation and analysis of two different users. Although repeatability estimates might have been improved by using

a single observer, our study design was chosen to best reflect the likely scenario when quantitative tractography is incorporated into clinical workflow. Finally, the inherent limitations of the tensor model should be acknowledged. The assumption that diffusivity in every voxel can be accurately described by a single ellipsoid is not always valid. The reliance of deterministic tracking algorithms on this model, therefore, compromises their ability to accurately characterize complex white matter architecture at the voxel/sub-voxel scale. Newer techniques, including high angular resolution diffusion imaging and diffusion spectrum imaging, are able to accommodate more complex probability displacement functions, allowing for more accurate tract construction.⁵⁰ For example, diffusion spectrum imaging has demonstrated the potential to resolve crossing white matter fibres.⁵¹ Interestingly, the reproducibility of mean MD and mean FA in our study is similar to that reported for comparable scalar metrics derived from diffusion spectrum imaging.⁴⁵

CONCLUSION

In conclusion, our study has demonstrated the test–retest repeatability of MD and FA derived from diffusion tractography. These data represent an advance in our understanding of the reproducibility of these metrics, which might one day serve to guide management in patients with localization-related epilepsy.

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