RESEARCH ARTICLE

Structure tensor informed fibre tractography at 3T

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Abstract

Structure tensor informed fibre tractography (STIFT) based on informing tractography for diffusion-weighted images at 3T and by utilising the structure tensor obtained from gradient-recalled echo (GRE) images at 7T is able to delineate fibres when seed voxels are placed close to the fibre boundaries. However, incorporating data from two different field strengths limits the applicability of STIFT. In this study, STIFT was implemented with both diffusion-weighted images and GRE images acquired at 3T. Instead of using the magnitude GRE data directly for STIFT as in the previous work, the utility of T_2^* maps and quantitative susceptibility maps derived from complex-valued GRE data to improve fibre delineation was explored. Single-seed tractography was performed and the results show that the optic radiation reconstructed with STIFT is more distinguishable from the inferior longitudinal fasciculus/inferior fronto-occipital fasciculus complex when compared to standard diffusion-weighted imaging tractography. We further investigated the quantitative effects of STIFT in a group of five healthy volunteers and evaluated its impact on measures of structural connectivity. The framework was extended to evaluate implementations of STIFT based on T_2^* -weighted and quantitative susceptibility-weighted images in a whole-brain connectivity study. In terms of connectivity, no systematic differences were found between STIFT and diffusion-weighted imaging tractography, suggesting that local improvements in tractography are not translated to the atlas-based structural connectivity analysis. Nevertheless, the reduction in the number of statistically significant connections in the STIFT connectivity matrix suggests that STIFT can potentially reduce the false-positive connections in fibre tractography.

KEYWORDS

diffusion weighted imaging, optic radiation, quantitative susceptibility mapping, structural connectivity, tractography

1 | INTRODUCTION

Diffusion-weighted imaging (DWI) is a versatile technique offering the ability to probe tissue microstructure through detection of water molecule diffusion within biological tissues. In white matter, the structure of axons creates an anisotropic diffusion medium which restricts the directions of water diffusion (Beaulieu, 2002). By measuring the diffusion-weighted signal, fibre orientations can be extracted in a voxel-wise manner using diffusion tensor imaging (Basser, Mattiello, & LeBihan, 1994a, 1994b) or other higher order models, such as q-ball imaging (Tuch, 2004) and spherical deconvolution (Anderson, 2005; Tournier et al., 2004, 2007). These fibre orientations can be subsequently used to reconstruct white matter pathways also known as fibre tracking or fibre tractography (Conturo et al., 1999; Jones et al., 1999; Mori et al., 1999). Applications of fibre tractography include

noninvasive visualisation of white matter architecture (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004), building the human brain connectome (Sotiropoulos & Zalesky, 2017) and white matter fibre tract segmentation for neurosurgery (Caverzasi et al., 2016).

Single-shot echo-planar imaging (EPI) acquisition is commonly used for DWI to reduce artefacts caused by macroscopic subject motion, and to enable the acquisition of a large number of diffusion orientations and/or shells within an acceptable acquisition time. However, EPI readout is subject to T_2^* signal decay, prohibiting long echo train lengths being used thus limiting the spatial resolution of DWI data. Therefore, a single image voxel can contain multiple fibre configurations such as kissing, bending and fanning fibres (Alexander, Hasan, Lazar, Tsuruda, & Parker, 2001; Frank, 2001; Tuch et al., 2002), and disentangling these fibre configurations remains challenging (Jbabdi & Johansen-Berg, 2011; Tournier, Mori, & Leemans, 2011). To achieve

higher spatial resolution DWI, it is possible to use segmented EPI acquisition at the expense of increased acquisition time and the phase coherence between multiple segments has to be carefully preserved (Butts et al., 1997; Guhaniyogi et al., 2016; Miller & Pauly, 2003; Porter & Heidemann, 2009; Williams et al., 1999).

Structure tensor informed fibre tractography (STIFT) based on diffusion images at 3T and gradient-recalled echo (GRE) images at 7T has been shown to improve the accuracy in tracking kissing, crossing as well as high curvature fibre tracts (Kleinnijenhuis, Barth, Alexander, van Cappellen van Walsum, & Norris, 2012). This method computes a structure tensor to detect the direction of local image gradient in high spatial resolution magnitude GRE images [where highly myelinated fibre bundles such as the optic radiation and cingulum can be distinguished at high field (Kleinnijenhuis et al., 2012)], making it harder for tracts to run between different fibre bundles. Accordingly, the directional information from the GRE structure tensor directly influences the tracking directions estimated from diffusion. Practically, the phase of GRE images also contains rich information about white matter tissue properties, as myelinated fibres are diamagnetic. White matter contrast can also be clearly visualised with susceptibility-weighted imaging (SWI) and quantitative susceptibility mapping (QSM) at high field MR (Liu, Li, Tong, Yeom, & Kuzminski, 2014), thus, these techniques have a potential for STIFT applications.

In the original STIFT implementation, diffusion-weighted images and GRE images were acquired on 3T and 7T scanners, respectively, limiting the applicability of STIFT. Meanwhile, improvements in scanner technology allow the acquisition of higher b values and techniques such as simultaneous multislice (SMS) acquisitions (Setsompop et al., 2012, 2013) allow more efficient data sampling, supporting higher angular resolution of DWI without significant increase of acquisition time. In this study, we set out to evaluate the performance of STIFT by utilising both DWI and GRE data at 3T with a state-of-the-art DWI sequence, along with not only the magnitude but also the phase of GRE signal as input to the structure tensor. Evaluation of STIFT performance was also extended beyond single fibre bundle tractography to a generalised whole-brain connectivity analysis.

2 | MATERIALS AND METHODS

2.1 | Data acquisition

Data acquisition was performed on a 3T scanner (Magnetom Prisma Fit, Siemens, Erlangen, Germany) using the manufacturer's 32-channel phased-array head coil in five healthy volunteers. The study was approved by the local ethics committee and each subject gave his informed consent. Data related to this study can be found at the Donders Repository via the following persistent link http://hdl.handle.net/11633/di.dccn.DSC_3015046.05_519.

The scanning session consisted of the following acquisitions:

- T_1 -weighted images were acquired using the MPRAGE sequence with the following parameters: TR/TE/TI = 2,300/3.03/1,100 ms, flip angle = 8° , matrix size = $256 \times 256 \times 192$ and resolution = 1 mm isotropic. Total acquisition time = 5 min 21 s.

- DWI data were acquired using a twice-refocused spin-echo EPI sequence with a multiband factor of 4 (Setsompop et al., 2012; Sotiropoulos et al., 2013) to improve sequence efficiency while achieving whole-brain coverage and bipolar gradient diffusion sensitisation was used to reduce eddy current effects (Reese, Heid, Weisskoff, & Wedeen, 2003). Main sequence parameters were: TR/TE = 3,460/97.6 ms, matrix size = $150 \times 150 \times 84$, resolution = 1.5 mm isotropic, bandwidth = 1,754 Hz/pixel, partial Fourier 6/8 and no extra in-plane acceleration. A single-shell sampling scheme with 100 evenly distributed diffusion directions was used with a b value of 2,000 s/mm², interleaved with 11 acquisitions without diffusion weighting. Total acquisition time = 6 min 41 s. Additionally, one EPI volume with no diffusion encoding was acquired with reversed phase encoding direction in order to correct for image distortions in the diffusion-weighted images;
- 3D multiecho gradient-recalled echo (mGRE) images were acquired with nonflow compensated monopolar gradients with the following parameters: TR = 52 ms, number of echoes of 5, TE = 5.6 ms to 44.8 ms with echo spacing of 9.8 ms, flip angle = 20° , 2D GRAPPA with an acceleration factor of 4 (2×2), matrix size = $256 \times 320 \times 176$ and resolution = 0.75 mm isotropic. Total acquisition time = 11 min 11 s.

2.2 | Data processing

2.2.1 | Preprocessing

T_1 -weighted images were processed with an anatomical processing pipeline fsl_anat based on FSL tools (www.fmrib.ox.ac.uk/fsl) including brain extraction, bias field correction, linear and nonlinear registration to the MNI152 space, and cortical/subcortical segmentation (Smith et al., 2004). The T_1 -weighted images were then interpolated using a trilinear method to match the spatial resolution of the mGRE data.

To provide high quality T_2^* maps and quantitative susceptibility maps, raw k -space data of the mGRE acquisition were exported from the scanner and offline image reconstruction was performed in MATLAB (MathWorks, Natick, MA) using methodologies to combine array coil images and to unwrap signal phase, ensuring no phase singularity was present in the phase images (Khabipova, Wiaux, Gruetter, & Marques, 2015; Robinson et al., 2017).

STIFT relies on the structural information obtained from the GRE images, but it is essential that this conveys information on white matter rather than veins (which also present strong T_2^* -weighted contrast). Therefore, venography was performed by applying a vesselness filter (Frangi, Niessen, Vincken, & Viergever, 1998) and a vessel enhancing diffusion filter (Manniesing, Viergever, & Niessen, 2006) with five iterations as suggested in Koopmans, Manniesing, Niessen, Viergever, and Barth (2008) on the root-mean-square of the mGRE images across echoes, such that the signal intensity of veins with diameter greater than 2 mm was enhanced. The venogram mask was subsequently derived by thresholding the above results, which in turn the large veins were excluded from structure tensor processing. Undesired image contrast caused by small veins and image noise in the mGRE images was mitigated by applying the spatially adaptive nonlocal means (ANLM) filter (Manjón, Coupé, Martí-Bonmatí, Collins, & Robles, 2010) to all echo images before T_2^* mapping, while the edges

between white matter tracts were preserved. T_2^* maps were then computed from the magnitude of the mGRE data and field maps were computed as in Khabipova et al. (2015). Using a single exponential decay model with a constant frequency shift over time, residual maps were generated so that voxels with high relative error (larger than 0.5) were excluded from further processing. The resulting T_2^* maps were thresholded by setting a minimum T_2^* of 20 ms and a maximum T_2^* of 120 ms ensuring that artefactual T_2^* values would not affect the structure tensor. The range of the resulting T_2^* maps was then rescaled to the new range between 0 and 1, implicitly forcing the first eigenvalue of the structure tensor to be approximately .05 at the optic radiation border.

To be able to use not only the information from the magnitude mGRE data but also the rich anatomical information from QSM, the background field contributions (associated with air-tissue interfaces and poor B0 shimming) were filtered out from the previously computed field maps using the Laplacian boundary value approach (Zhou, Liu, Spincemille, & Wang, 2014). The resulting local field maps were then used to compute magnetic susceptibility maps in a two-step process. In the first iteration, the (modulated) closed-form solution was used, as it can quickly compute the optimum smoothness regularisation value based on the L-curve approach (Bilgic et al., 2014). Subsequently, this method was converted into the following optimisation problem which can be solved by the iterative LSQR method (Li et al., 2015):

$$\arg \min_{\chi} \|W(F^{-1}DF\chi - \phi)\|_2^2 + \lambda \|W\nabla\chi\|_2^2 \quad (1)$$

where F and F^{-1} are the discrete forward and inverse Fourier transform operators, D is the dipole kernel, χ contains the tissue susceptibility values and ϕ is the local field map. λ is the regularisation parameter derived from the L-curve approach, controlling the smoothness constraint imposed by the 3D gradient operator ∇ on the estimated tissue susceptibility map. The weighting matrix W was calculated based on the multiplication of the extrapolated signal S_0 at $TE = 0$ and the relative error, which were both derived from the T_2^* maps, as follows:

$$W = \begin{cases} S_0 \left(1 - \frac{\text{relative error}}{0.1}\right), & \text{relative error} \leq 0.1 \\ 0, & \text{relative error} > 0.1 \end{cases} \quad (2)$$

This was done to ensure that regions where the signal does not obey the biophysical model or that have very low SNR cannot create artefacts in QSM.

To further enhance the contrast of white matter structures, diamagnetic features predominant in white matter were extracted from the quantitative susceptibility maps and combined with the rescaled T_2^* maps, creating diamagnetic susceptibility map-weighted images (dSMWI) (Gho et al., 2014). The following equation was used in this process:

$$\text{dSMWI} = W_{\chi^-} \times T_{2^*}^{\text{rescaled}} \quad (3)$$

where W_{χ^-} is the weight derived by normalising the diamagnetic tissue in the susceptibility maps with values chosen to include most of

the splenium of the corpus callosum as shown in the following equation:

$$W_{\chi^-} = \begin{cases} 1, & \chi > .039 \text{ ppm} \\ \frac{\chi + 0.117}{0.156}, & -0.117 \text{ ppm} \leq \chi \leq .039 \text{ ppm} \\ 0, & \chi < -0.117 \text{ ppm} \end{cases} \quad (4)$$

Diffusion-weighted images were corrected for eddy current distortion and susceptibility-induced distortion in FSL by using eddy_correct (FSL's earlier tool for eddy current correction) and topup tools (Andersson & Sotiropoulos, 2016; Andersson et al., 2003; Smith et al., 2004). The distortion-corrected images were then interpolated using the trilinear method to match with the spatial resolution of the mGRE data. The diffusion probability density function was subsequently estimated using a ball-and-stick model (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007), allowing extraction of maximally three fibre orientations in each voxel.

Anatomical structure alignment between the mGRE images and diffusion-weighted images was achieved by two co-registration steps: a linear transformation matrix from T_1 space to diffusion space was obtained by registering the interpolated T_1 -weighted images to the interpolated EPI images without diffusion weighting. A second linear transformation matrix was derived from the co-registration of the first echo of the mGRE data and the interpolated T_1 -weighted data. The rescaled T_2^* maps, dSMWI images and various masks were then transformed to diffusion space by applying the transformation matrices associated with these two steps.

Brain parcellation was performed by registration of the Jülich histological atlas (Eickhoff et al., 2005), provided with FSL, to the diffusion space. This was achieved by registration of MNI152 2-mm T_1 -weighted images to the acquired T_1 -weighted images (in the diffusion space) using the aforementioned nonlinear process (which was performed with fsl_anat preprocessing), subsequently this transformation was applied to the histological atlas resulting in subject-specific cortical and subcortical labels. These labels were regarded as the network nodes to determine the structural connectivity by tractography.

2.2.2 | Structure tensor and STIFT algorithm

Structure tensors were calculated by applying a three-dimensional Sobel-like filter to the rescaled T_2^* maps and dSMWI images, respectively, such that the first eigenvector of the structure tensor $\mathbf{V}_{ST}$ provides the direction of local signal intensity gradient, while the first eigenvalue of the structure tensor λ_{VST} provides the strength of the gradient intensity (Brox et al., 2006). To incorporate the structure tensor directional information into the tractography process, all fibre orientations estimated from the ball-and-stick model were used as the input of the STIFT algorithm. For each voxel, the diffusion fibre orientations $\mathbf{V}_{DWI}$ were first rotated towards the plane perpendicular to the first eigenvector of the structure tensor, $\mathbf{V}_{ST}$, by calculating the cross product of these two vectors (Kleinnijenhuis et al., 2012). The resulting vector was subsequently used to rotate the first eigenvector of the structure tensor $\mathbf{V}_{ST}$ towards the plane orthogonal to the structure tensor through a second cross product. The final adapted fibre orientation $\mathbf{FO}_{STIFT}$ is the vector sum of the original diffusion fibre

orientation and the adapted structure tensor direction, weighted by the first eigenvalue of the structure tensor at the optic radiation border λ_{OR} :

$$FO_{STIFT} = (1 - \lambda_w) V_{DWI} + \lambda_w [V_{ST} \times (V_{DWI} \times V_{ST})] \quad (5)$$

where

$$\lambda_w = \begin{cases} 1, & \lambda_{V_{ST}} > \lambda_{OR} \\ \frac{\lambda_{V_{ST}}}{\lambda_{OR}}, & \lambda_{V_{ST}} \leq \lambda_{OR} \end{cases}$$

The process and its motivation are described in greater detail in Kleinnijenhuis et al. (2012). The structure tensor-adapted fibre orientation maps derived from the STIFT algorithm were used in the subsequent fibre tractography analysis. The summary of the data processing can also be visualised in Figure 1.

2.2.3 | Tractography

To evaluate the utility of 3T-only STIFT in the context of tractography, we devised three evaluation strategies:

1. Following the protocol used in the first demonstration of STIFT (Kleinnijenhuis et al., 2012), where voxels inside of and on the border of the optic radiation and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (ILF/IFOF) complex were used as seeds to visualise if STIFT helped delineate these tracts.
2. As the most beneficial results shown with STIFT were found in the visualisation of the optic radiation, we tested specifically the hypothesis of improved connectivity between the lateral geniculate nucleus (LGN) and primary visual cortex (V1).
3. A common application of DWI is the creation of structural connectivity matrix, we therefore evaluated the impact of STIFT on whole-brain connectivity matrices.

Bayesian-based probabilistic tractography (FSL's probtrackx tool) was performed on all five subjects to generate the single-seed tractograms and to compare the connectivity strength between DWI fibre tractography and STIFT. Connectivity strength between any two network nodes was defined as the ratio of the number of streamlines connecting the nodes to the total number of the generated streamlines to minimise the connectivity variation due to neuroanatomical differences of the participants.

Single-seed tractography in white matter bundles and their boundaries

Four consecutive voxels were used as seeds. They were placed so that the outer seeds were inside the optic radiation or the ILF/IFOF complex, and two middle seeds were on the borders of the optic radiation or ILF/IFOF (as shown in Figure 2), similar to the approach used in Kleinnijenhuis et al. (2012). This process was repeated for all five subjects. A grey matter mask segmented from the T_1 -weighted data was used as the target mask. Tractography was performed on each seed separately and 5,000 fibre streamlines were generated per seed. Fibre curvature threshold was set to 90° . FSL's probtrackx tool produced a map of the number of streamlines passing through image voxels and this result was used to generate a 3D surface of the reconstructed

fibre tract. A threshold of 100 streamlines passing through a voxel was applied to reduce possible false-positive streamlines of each tractography application.

LGN-V1 connectivity

To compute the connectivity between the LGN and V1, the entire LGN was defined as the seed region based on the labels of the Jülich histological atlas. Tractography was performed on the right and left hemispheres separately for all subjects, with 5,000 streamlines generated per seed and a fibre curvature threshold of 90° applied. By setting V1 as both the tractography target and stopping region, the number of streamlines reaching V1 was recorded without being repeatedly counted.

Whole-brain connectivity study

Whole-brain connectivity matrices of each subject were created by using all white matter voxels segmented from the T_1 -weighted images as seeds to produce 500 streamlines per voxel with a fibre curvature threshold of 90° and all grey matter defined as both connectivity and streamline termination targets. In addition to the labels available from the Jülich histological atlas, which has 103 grey matter regions in total, an extra node representing the brainstem was added to measure its related connectivity from the rest of the brain regions. To understand the major effects of STIFT, we only focused on the comparisons of the 10 strongest connections measured without STIFT adaptation and 10 connections with the greatest change of connectivity between DWI tractography and STIFT across subjects. Analysis was also conducted to compare the connectivity between DWI tractography and STIFT on the 10 strongest connections without STIFT adaptation for the V1- and brainstem-related pathways.

2.3 | Statistical analysis

Two-sample t tests were conducted to compare the structural connectivity between DWI tractography and STIFT in MATLAB. A statistically significant finding was defined as a p value of less than .05 for the comparison on the LGN-V1 connectivity. For the whole-brain connectivity application, since we focused on 10 specific connections in each statistical test, finding with a p value of less than .005 was considered as statistically significant based on the Bonferroni correction of 10 comparisons.

3 | RESULTS

For visualisation purposes, Figure 3 shows some of the derived images from our data set including the grey-white matter mask (Figure 3d) obtained from the T_1 -weighted image (Figure 3a), the venogram (Figure 3e) derived from the mGRE data (Figure 3b), and the colour-coded map of the most populated fibre orientations (as estimated using the ball-and-stick model, Figure 3f) derived from our high-resolution DWI acquisition (Figure 3c). Note that each data set had a different initial spatial resolution and all the masks and derived images were computed in the mGRE high-resolution space (0.75 mm isotropic).

FIGURE 1 Summary of data processing. MATLAB (orange) and FSL (green) were used to process the data. Multiecho GRE and T_1 -weighted data were initially processed in their own spaces. The input of the STIFT formalism from mGRE and T_1 -weighted data processing results (including the structure tensors derived from either dSMWI images or the rescaled T_2^* maps, the STIFT exclusion mask and the tissue classification masks WM/GM/CSF) were registered to the diffusion space where the STIFT formalism was then applied. The output of the STIFT algorithm was the STIFT adapted fibre orientations (STIFT- T_2^* and STIFT-dSMWI), which were compared with the standard diffusion fibre orientations in different tractography applications [Color figure can be viewed at wileyonlinelibrary.com]

Figure 4 shows representative transverse and coronal slices of the data used to compute the structure tensors, namely the: quantitative susceptibility maps (Figure 4a), rescaled T_2^* maps (Figure 4b) and dSMWI images (Figure 4c) computed from the mGRE data. The contrast between the optic radiation and ILF/IFOF can be observed in

both T_2^* maps and quantitative susceptibility maps, but on the susceptibility maps it is extended to the posterior part of the optic radiation towards the V1 (see green arrows). Fibre bundles such as the corticospinal tracts can be clearly identified in the susceptibility maps but not in the T_2^* maps (see blue arrows). As a result, the dSMWI

FIGURE 2 An illustration of STIFT formalism. The left image shows the most populated diffusion fibre orientations (blue sticks), the first eigenvector of the structure tensors (green sticks) and the STIFT-adapted fibre orientations by integrating the structure tensor information to the diffusion fibre orientations (orange sticks). All sticks shown here are the in-plane component of the corresponding vectors. Image in the lower right corner shows an example of seeds for the single-seed tractography to reconstruct the optic radiation (OR) and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (ILF/IFOF) for Subject 1. Similar strategy was applied to define the seeds for all five subjects. The same colour scheme was used to display corresponding bundles in Figures 5 and 6 [Color figure can be viewed at wileyonlinelibrary.com]

images show a mixed white matter contrast of both T_2^* maps and susceptibility maps. Such features are manifested as more and sharper edges in the first eigenvalue maps of the dSMWI structure tensor (Figure 4f) compared to that of the T_2^* structure tensor (Figure 4e). Furthermore, the dSMWI images clearly show a weaker contrast between the deep grey matter structures and their surrounding white matter tissue, which can also be seen in the derived structure tensor

FIGURE 3 An illustration of data quality. (a) Sample interpolated T_1 -weighted image, (b) first echo image from the mGRE data, (c) interpolated DWI image, (d) segmentation result from T_1 -weighted data (grey: grey matter; white: white matter; black: background and cerebrospinal fluid), (e) maximum intensity projection of the venogram on a 6.75 mm slab obtained from the mGRE data set, and (f) anisotropic volume fraction modulated, RGB-encoded most populated fibre orientation map estimated by a ball-and-stick model [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 4 T_2^* mapping and diamagnetic susceptibility map-weighted imaging results and their corresponding structure tensors.

(a) Quantitative susceptibility map, (b) rescaled T_2^* map, (c) dSMWI image by combining the susceptibility map and the rescaled T_2^* map using Equations (3) and (4), (d) overlay of the grey matter mask (light blue), venogram mask (blue), relative error masks (red), and final exclusion mask (orange) for the STIFT adaptation after applying the structure tensor on the dSMWI image, (e) the first eigenvalue of the rescaled T_2^* structure tensor, and (f) the first eigenvalue of the dSMWI structure tensor. Note that the dSMWI image demonstrates image contrasts in the corticospinal tracts (see blue arrows) and in the posterior part of the optic radiation (see green arrows) which are absent in the T_2^* map [Color figure can be viewed at wileyonlinelibrary.com]

figures. It is still important to make sure these edges are not considered in the STIFT algorithm. To ensure the STIFT correction does not prevent white matter tracts from entering (deep) grey matter, the STIFT algorithm exclusion mask, based on the combination of the grey matter mask (light blue in Figure 4d), venogram mask (blue in Figure 4d), and relative error mask (red in Figure 4d), was expanded by an amount equal to the width of the kernel used to compute the structure tensor. This resulted in the exclusion mask represented in orange in Figure 4d, which shows that the STIFT correction (Equation (5)) was only applied in white matter regions away from tissue borders (seen in grey).

The first evaluation of the performance of STIFT proposed in the "Materials and Methods" section was the differentiation of the optic radiation from ILF/IFOF complex, particularly for voxels that are close to the border of these fibre bundles. The STIFT technique was

FIGURE 5 Tractograms of the optic radiation and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus of Subject 1. Results shown here were obtained from standard DWI data (first column), the T_2^* map-derived STIFT (second column) and the dSMWI image-derived STIFT (third column). The first and third rows are shown in dorsal view while the second and fourth rows are in oblique sagittal view. The fibre bundles were obtained using four neighbouring seeds (see Figure 2) located close to the border between the optic radiation and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (ILF/IFOF) complex. The top two rows show examples of white matter voxels immediately adjacent to the border (green bundle: seed close to the optic radiation; red bundle: seed close to the ILF/IFOF complex, both ILF and IFOF were reconstructed for all methods with this seed) while the bottom two rows show tractograms where the seeds are one voxel away from the border (yellow bundle: seed within the optic radiation; blue bundle: seed within the ILF/IFOF complex and all methods tracked ILF; colours are consistent with Figure 2). It is clear that the anterior part of the optic radiation is more pronounced with STIFT (see black arrows) in contrast to DWI tractography. However, there is also an increase of false-positive streamlines for both green bundles of STIFT- T_2^* that tracked along the IFOF and red bundles of the two STIFT methods that tracked non-ILF/IFOF structures (see red arrows) [Color figure can be viewed at wileyonlinelibrary.com]

evaluated in its two flavours: STIFT- T_2^* (adapted fibre orientations based on the rescaled T_2^* structure tensor) and STIFT-dSMWI (adapted fibre orientations based on diamagnetic SMWI structure tensor). The output of the single-seed tractography with seed locations shown in Figure 2 is a map with the number of streamlines passing through a given image voxel. For visualisation purposes, the results of the single-seed tractography were thresholded to create a 3D surface representing the reconstructed fibre bundles shown in Figures 5 and

6 for all subjects. In most cases, Meyer's loop (the anterior part of the optic radiation) can be identified with STIFT-dSMWI (4/5 subjects have a visible Meyers loop with the yellow seed) or STIFT- T_2^* (3/5 subjects) but not in diffusion tractography (2/5 subjects) even though the seed was placed clearly inside the optic radiation (yellow bundles in Figures 5 and 6). All three methods reconstructed similar ILF/IFOF (blue bundles in Figures 5 and 6) when the seed was placed in this fibre bundle. Substantial differences between the three methods can also be observed in the fibre bundles with the seeds placed on the border of the optic radiation and ILF/IFOF (green and red bundles in Figures 5 and 6). Using only diffusion data, the tracts reconstructed from the two closely placed seeds are often very similar and bending of Meyer's loop is not easily observed (ML only observable in one out of five subjects) from the tract closer to the optic radiation (green bundles). STIFT- T_2^* and STIFT-dSMWI results provide more differentiable tracts in general, with Meyer's loop most often being clearly identified even when the seed was placed on the border close to the optic radiation (see black arrows on green bundles) resulting in three out of five observations for both STIFT- T_2^* and STIFT-dSMWI. However, the STIFT tractograms of Subjects 2 and 3 also show an increase of ILF/IFOF streamlines on the same (green) bundles. Although the ILF/IFOF reconstructed with STIFT are more distinguishable from the optic radiation when seeds were placed on the fibre border (red bundles in Figures 5 and 6), both increase of false-positive streamlines (see red arrows in Figures 5 and 6) and decrease of true-positive streamlines (see red arrows in Figure 6) of ILF/IFOF were observed with STIFT.

After this anecdotal evidence suggesting that the dSMWI images, in our limited sample size, improve the tractography of the optic radiation, we evaluated the connectivity between the LGN and V1 across subjects. These regions were defined on each subject by the atlas-based approach. Table 1 shows the structural connectivity between the LGN and V1 with and without STIFT adaptation. For both hemispheres, no significant difference in connectivity was observed for STIFT- T_2^* and STIFT-dSMWI compared to the DWI tractography.

When expanding the analysis to consider the whole-brain tractography, no noticeable differences could be observed in the connectivity matrices (see Figure 7). One potential explanation is that with STIFT there could be a reduction of false-positive connections. We expected that false-positive connections would correspond to a relatively weak connectivity close to zero. Therefore, one-sample *t* tests were performed on all connections of the connectivity matrices to compare their mean connectivity strength across subjects to the expected mean of zero. Those connections with a *p* value equal to or greater than .05 were regarded as false positives and discarded from further analysis. Based on this criterion, the number of remaining connections with DWI tractography is 1850, while with STIFT- T_2^* is 1,706 and with STIFT-dSMWI is 1,612. Interestingly, most of the false positives were found to be interhemispheric (which accounted for 54.9%, 56.6%, and 55.9% of thresholded connections in the cases of the DWI tractography, STIFT- T_2^* and STIFT-dSMWI).

After thresholding the connectivity matrices, only connections that were common to all tractography methods were compared. The connectivity strength of the 10 strongest connections from the

FIGURE 6 Tractograms of the optic radiation and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (ILF/IOF) of the four subjects not shown in Figure 5. Fibre tracts of diffusion tractography and STIFT (mirrored) with seeds placed within the optic radiation and ILF/IOF complex (first and second columns) and on the border between the fibre bundles (third and fourth columns). The same colour scheme is used to display the fibre tracts with the seed locations similar to Figure 2. When the seeds were placed clearly inside the optic radiation, the yellow fibre bundles generated with STIFT- T_2^* provides better visualisation of the anterior part of optic radiation in Subjects 3 and 4 compared to DWI tractography while the STIFT-dSMWI results show improvement in Subjects 3 and 5. ILF was reconstructed with the blue seed in Subjects 2–4 while the seed with the same colour generated IFOF in Subject 5. The tractograms of the seeds on the border of the optic radiation and ILF/IOF shows a mixed positive and negative impact of STIFT. Meyer's loop of the optic radiation is generally more distinguishable with both STIFT- T_2^* and STIFT-dSMWI for the seed placed close to the optic radiation (see black arrows on the green bundles of Subjects 2–4). However, extensions of ILF and IFOF reconstructed by STIFT were also observed in the same bundle in Subjects 2 and 3 (see red arrows). In addition, the anterior portion of the IFOF reconstructed with STIFT- T_2^* (red bundles) in Subject 5 is diminished, indicating that the STIFT algorithm made an excessive correction in this case [Color figure can be viewed at wileyonlinelibrary.com]

whole-brain tractography are shown in Table 2. The majority of the 10 connections are motor-related and visual-related connections. No significant difference in connectivity was found between the DWI tractography and STIFT. The 10 connections with the greatest changes in connectivity between the DWI tractography and STIFT are

shown in S1 Table (see Supporting Information for more details). It can be seen that none of these changes has a p value that survives the Bonferroni correction.

The connectivity strength on the 10 strongest connections related to the V1 and to the brainstem are shown in S2 Table

TABLE 1 Connectivity strength of the LGN-V1 connection across subjects

Hemisphere	Connectivity strength (10^{-3})			p value	
	DWI	STIFT- T_2^*	STIFT-dSMWI	STIFT- T_2^*	STIFT-dSMWI
Left	68.16 $\pm$ 12.90	85.54 $\pm$ 21.95	70.56 $\pm$ 16.39	0.51	0.91
Right	76.94 $\pm$ 7.62	72.75 $\pm$ 11.25	63.73 $\pm$ 6.36	0.76	0.22

No connectivity difference was found between the DWI tractography and STIFT in the LGN-V1 connection. Connectivity strength are mean $\pm$ SE.

FIGURE 7 Whole-brain connectivity matrices of STIFT and DWI tractography. Structural connectivity matrices of (a) DWI tractography, (b) T_2^* map-derived STIFT, and (c) dSMWI image-derived STIFT. The upper triangle of the matrices represents the mean connectivity strength across subjects (red: strong connection; blue: weak connection). The lower triangle represents the remaining connections (in red) after thresholded the connections with a p value less than .05 in the one-sample t test comparing the group mean connectivity strength to the expected mean of zero [Color figure can be viewed at wileyonlinelibrary.com]

(see Supporting Information). This subset of data provides a quantitative measure of STIFT in regions where the structure tensors gave additional anatomical information: the optic radiation and corticospinal tracts. No significant connectivity difference was found between the DWI tractography and STIFT for these two analyses.

4 | DISCUSSION

In this study, we were able to reproduce some of the findings reported in Kleinnijenhuis et al. (2012), including tracking the optic radiation via Meyer's loop, especially for seeds close to the fibre bundle border between the optic radiation and ILF/IFOF, reflecting the neuroanatomical features which are problematic for conventional DWI tractography due to the highly curved nature of Meyer's loop. These results are consistent with the previous findings (Kleinnijenhuis et al., 2012) but are obtained solely with 3T data in contrast to the previous study that combined 3T DWI and 7T GRE data. In the analysis shown in Figures 5 and 6, the seeds are already located in an interpolated space (at 0.75 mm isotropic resolution), so some degree of partial volume effect is bound to exist between neighbouring seeds given that the data were acquired at 1.5 mm isotropic. STIFT tries to bring some extra structural information to this interpolation process.

Although STIFT generally demonstrates better delineation of the optic radiation from ILF/IFOF, it should also be noted that both positive and negative results were obtained with STIFT, in particular tracking the ILF/IFOF near the optic radiation border where reduction of true-positive results were observed in some instances.

In principle, any image providing contrast between white matter fibre bundles can be used as input for the structure tensor. Here, we have demonstrated an extension of the STIFT formalism to include both T_2^* maps and quantitative susceptibility maps. With the rapid development of QSM in recent years, it is more feasible to obtain high-quality magnetic susceptibility maps with reduced image artefacts from GRE phase images (Li et al., 2015; Liu et al., 2012). Incorporating diamagnetic masks generated from QSM with T_2^* maps where white matter contrast already exists, the resulting dSMWI images further enhance the contrast of the optic radiation and corticospinal tracts, as previously demonstrated (Gho et al., 2014). This provides extra anatomical information to the structure tensor such that these fibre tracts can be better delineated.

According to the previous findings (and the mechanism of STIFT), it is expected that the impact of STIFT should be the strongest when tracking voxels close to fibre borders, while the tracking behaviour of STIFT is similar to that of the DWI tractography for voxels within fibre

TABLE 2 Structural connectivity with the 10 strongest connections in the DWI tractography and their strength with STIFT in the whole-brain tractography

Node	Node	Connectivity strength (10^{-3})			p value	
		DWI	STIFT- T_2^*	STIFT-dSMWI	STIFT- T_2^*	STIFT-dSMWI
Premotor cortex L	Premotor cortex R	12.44 ± 1.16	12.90 ± 0.88	9.93 ± 1.34	0.76	0.20
Visual cortex V1 R	Visual cortex V2 R	6.01 ± 0.47	6.14 ± 0.49	6.03 ± 0.49	0.85	0.98
Visual cortex V1 L	Visual cortex V2 L	4.19 ± 0.47	4.30 ± 0.54	4.27 ± 0.46	0.89	0.91
Broca's area BA44 L	Premotor cortex L	2.94 ± 0.33	2.74 ± 0.37	2.50 ± 0.31	0.69	0.36
Broca's area BA44 R	Premotor cortex R	2.34 ± 0.44	2.33 ± 0.43	2.17 ± 0.48	0.99	0.81
Broca's area BA44 L	Broca's area BA45 L	1.75 ± 0.18	1.90 ± 0.21	1.87 ± 0.22	0.61	0.70
Visual cortex V2 R	Visual cortex V3V R	$1.75 \pm .07$	$1.76 \pm .09$	$1.83 \pm .09$	0.96	0.48
Visual cortex V2 L	Visual cortex V3V L	1.68 ± 0.21	1.68 ± 0.23	1.74 ± 0.22	0.98	0.87
Visual cortex V2 L	Visual cortex V4 L	1.55 ± 0.23	1.51 ± 0.21	1.50 ± 0.22	0.89	0.89
Visual cortex V3V L	Visual cortex V4 L	1.38 ± 0.18	1.40 ± 0.18	1.45 ± 0.18	0.95	0.79

Connectivity strength are mean $\pm$ SE.

bundles (where no additional structural information is available) (Kleinnijenhuis et al., 2012). In the whole-brain connectivity analysis, all white matter voxels were used to create the connectivity matrix. As the majority of voxels are located inside the fibre bundles or in the STIFT exclusion mask, the positive effect of STIFT becomes less clear. Although no statistical connectivity differences were found between DWI tractography and STIFT, our results do not invalidate the previous findings.

Another factor that contributed to a reduced impact of our implementation of STIFT is related to the technical developments of DWI. Diffusion acquisition protocols have significantly improved over the last decade, with the introduction of SMS imaging (which allows more efficient acquisition) and the increase of gradient specifications which support higher spatial resolution data acquisition (when compared to the previous study the spatial resolution went from 2 mm to 1.5 mm isotropic) with similar echo times (TE of 95 ms with an acceleration factor of 2 was used in the previous study compared to TE of 97.6 ms with partial Fourier 6/8 in this study) and at higher angular resolution. Conversely, acquiring all the data at 3T means that the spatial resolution of mGRE data was restricted by the acceptable duration of the data acquisition, with the optimum echo times increasing with respect to the previous study and the base SNR decreasing (Marques & Norris, 2018). This combination of factors resulted in the GRE data acquired with an eightfold smaller voxel volume than the DWI voxels (while in the previous study it was 64-fold). Therefore, it is possible that these two factors together reduced the effectiveness of STIFT at 3T which now has less prior information to add to the interpolation process of the DWI data. Alternatively, all experiments could be conducted on a 7T scanner allowing higher spatial resolution GRE data to be acquired. Yet DWI remains a very challenging endeavour at 7T, mainly due to the increased B1+ and B0 field inhomogeneities (the latter resulting in increased distortion artefacts introduced by susceptibility changes at air-tissue interfaces) and the increased power deposition that makes SMS spin echo imaging close to prohibitive at 7T (Gallichan, 2018; Marques & Norris, 2018).

Interestingly, we observed a decrease in the number of statistically significant bundles upon applying STIFT (see Figure 7). This could be interpreted in two ways: (a) STIFT has reduced the number of significant bundles by increasing the variance across subjects; (b) STIFT has effectively reduced the number of false-positive connections in the brain, particularly interhemispheric connections. Given the lack of a ground truth connectivity matrix, it is not possible to disambiguate between these two possible explanations.

Our study of the generalisability of STIFT to other brain regions using the connectivity matrix has some limitations. The metric used to compute the strength of structural connectivity is affected not only by the distance between two network nodes but also parameters like the size of the nodes. Consequently, structural differences such as brain size and folding pattern of the cortical surface across individuals added variability to our comparisons (Sporns, 2013), though we tried to alleviate this issue by normalising the connectivity strength individually. More importantly, atlas-based cortical/subcortical segmentation was used to obtain the network nodes as our tractography targets, which may not be accurate enough to represent the brain structures of the participants. Particularly, STIFT is expected to improve

tractography of white matter in regions close to the bundle boundary which could be expected to connect the edge of a given cortical region. For example, fibres in the lateral aspect of the optic radiation are expected to connect the side edges of the LGN and V1. Therefore, misalignment between the atlas labels and the actual cortical/subcortical regions of each individual participant can result in an inability to capture the effects of STIFT. One possibility to reduce the misalignment effect is to acquire resting-state fMRI data, from which subject-specific cortical regions can be parcellated (Blumensath et al., 2013; Cloutman & Lambon Ralph, 2012).

5 | CONCLUSION

We have demonstrated that both 3T DWI and GRE data can be used for STIFT to produce comparable results as in the original study utilising data collected at 3T and 7T, respectively. In addition to the magnitude of GRE data, the phase of GRE also possesses strong white matter contrast that can be used for STIFT applications and has been demonstrated to improve the visualisation of Meyer's loop. In the more quantitative analysis of our small cohort, none of the STIFT implementations showed clear benefits, even when addressing the specific question of the connectivity between LGN and V1, which contains the same fibres presented as anecdotal evidence of improvement. Although no statistically significant structural connectivity differences were observed between DWI tractography and STIFT in this study, the decrease of statistically significant entries in the connectivity matrix suggests that this could potentially result in reduced number of false-positive connections. Further research is needed to understand the impact of STIFT in connectivity studies and the importance of using subject-specific parcellation of the cortex.

AUTHOR CONTRIBUTIONS

Conceptualization, K.-S.C., D.G.N. and J.P.M.; Methodology, K.-S.C., D.G.N. and J.P.M.; Software, K.-S.C. and J.P.M.; Formal Analysis, K.-S.C.; Investigation, K.-S.C. and J.P.M.; Writing – Original Draft, K.-S.C., J.P.M. and D.G.N.; Writing – Review & Editing, K.-S.C., J.P.M. and D.G.N.; Supervision, J.P.M. and D.G.N.; Funding Acquisition, D.G.N., J.P.M.

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SUPPORTING INFORMATION

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