Generalisation of continuous time random walk to anomalous diffusion MRI models with an age-related evaluation of human white matter

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ABSTRACT

Diffusion MRI measures of the human brain provide key insight into microstructural variations across individuals and into the impact of central nervous system diseases and disorders. One approach to extract information from diffusion signals has been to use biologically relevant analytical models to link millimetre scale diffusion MRI measures with microscale influences. The other approach has been to represent diffusion as an anomalous process and infer information from the different anomalous diffusion equation parameters. How parameters of various anomalous diffusion models vary with age in the human brain white matter has not been investigated. We perform the tests within a general continuous time random walk framework, in which temporal jump lengths and structural barriers to diffusion are considered. We outline the formulations for the super-diffusion (i.e., stretched exponential), sub-diffusion, quasi-diffusion and fractional Bloch-Torrey models with respect to the continuous time random walk expression. We also provide a direct link between diffusion kurtosis and the sub-diffusion model and demonstrate mathematical equivalence between parameters. 7T diffusion weighted MRI data in the age range 19-67 was used in this study, particularly focusing on the corpus callosum. Anomalous diffusion model parameters were found to show trends with aging, and interestingly, our investigations led to a new robust technique for generating maps of diffusion kurtosis.

KEYWORDS: diffusion MRI, white matter, aging, continuous time random walk, anomalous diffusion, diffusional kurtosis imaging, high b-value
1 INTRODUCTION

Diffusion MRI (dMRI) provides a mechanism by which microscopic water diffusion in tissue can be probed. Diffusion-weighted MRI signals from tissue, such as the human brain, are obtained by varying the diffusion weighting in the dMRI protocol - primarily the duration, separation and strength of the diffusion gradient is changed to change sensitisation to diffusion. To make a link between mm-scale measurements, and the micro-scale water interactions within tissue, mathematical models have widely been adopted to describe the expected diffusion signal behaviour. Through model parameter variations, in vivo information on tissue microstructure, such as bulk tissue diffusivity, anisotropy, structure symmetry and directional diffusivity (Basser et al., 1994), axon radius (Assaf et al., 2008), neurite orientation and density (Zhang et al., 2012) and level of diffusion kurtosis (Jensen et al., 2005) have been able to be inferred from dMRI measurements. Extensive applications of dMRI have been reported in the brain (Johansen-Berg and Behrens, 2014; Jones, 2010) and for other body parts (Brancato et al., 2019; Khoo et al., 2011; Miller et al., 2004; Taouli and Koh, 2009). The clinically routine use of dMRI in the clinic underpins the importance of this MRI contrast mechanism (González et al., 1999; Warach et al., 1995).

Whilst existing models have been derived based on the classical diffusion process with consideration given to the domain in which diffusion occurs, models capturing the anomalous nature of diffusion in tissue based on continuous time random walk (CTRW) theory (Klages et al., 2008; Metzler and Klafter, 2000) have been proposed as well. The primary difference between the two approaches lies in how the problem is considered. In the former, a physiological property is generally identified, and tissue geometry is incorporated into the model formulation. As such, a specific model parameter is assumed to relate directly to the property of interest, such as water compartments, axon diameter, neurite density, intra- and extra-cellular volume fractions (e.g. bi-exponential (Clark and Le Bihan, 2000), CHARMED(Assaf and Basser, 2005), AxCaliber(Assaf et al., 2008), ActiveAx(Alexander et al., 2010), NODDI (Zhang et al., 2012), VERDICT (Panagiotaki et al., 2015)). The second approach makes no microstructure assumptions but instead considers diffusion within a hindered and restricted micro-environment, wherein the mean-squared displacement of diffusion spins follows a power-law relaxation.
in time, and the power is described by the competition between processes characterised by fractional in space ($\alpha$) and/or fractional in time ($\beta$) where $\alpha$ represents the probability density function (pdf) of jump lengths of diffusion spins and $\beta$ represents the pdf of waiting times between jumps.

The continuous time random walk (CTRW) framework was recently applied in the context of dMRI, wherein time and space fractional components are considered together (Gatto et al., 2019; Ingo et al., 2015, 2014; Karaman et al., 2016; Magin et al., 2014; Tang and Zhou, 2019; Yang et al., 2020; Yu et al., 2018; Zhong et al., 2019). Other anomalous diffusion models for dMR include the super-diffusion (i.e., stretched exponential) (Bennett et al., 2003; Capuani et al., 2013; Hall and Barrick, 2008; Palombo et al., 2011), sub-diffusion (Bueno-Orovio et al., 2016; Capuani et al., 2013; Palombo et al., 2011), quasi-diffusion (Barrick et al., 2020), and fractional Bloch-Torrey (Magin et al., 2008) models. In principle, the CTRW model is very flexible, and should be able to be used to describe other anomalous diffusion processes. One motivation herein is to frame existing anomalous diffusion models within the CTRW framework to help describe differences between the various models. It is then natural to assess how model parameters differ in tissue, and how well models are able to fit the data.

Our primary aim here is to provide insight into how anomalous diffusion models and their parameters behave in white matter with aging, and to promote the use of anomalous diffusion models in probing tissue microstructure. In addition, we seek to establish a direct link between the diffusion kurtosis imaging (DKI) formula (Jensen et al., 2005) and the sub-diffusion model (Bueno-Orovio et al., 2016; Capuani et al., 2013; Palombo et al., 2011) and provide a new alternative and explicit way of computing kurtosis and apparent diffusivity.

2 THEORY

In this section, we describe the theory of continuous time random walk (CTRW) model and describe how commonly used anomalous diffusion models can be classified under the CTRW framework.

2.1 CTRW-MRI modelling framework

In the context of CTRW theory, the jump lengths and waiting times of diffusing particles (walkers) follow probability distributions with infinite variance in contrast to the finite variance for Gaussian
distribution in the context of classical random walk (Metzler and Klafter, 2000). The motion of CTRW particles in heterogeneous media can be described by a time-space fractional diffusion equation:

\[
\frac{\partial^\beta P(x,t)}{\partial t^\beta} = D_{\alpha,\beta} \frac{\partial^{2\alpha} P(x,t)}{\partial |x|^{2\alpha}}, \quad 0 < \beta \leq 1, \quad \frac{1}{2} < \alpha \leq 1,
\]

(1)

where \( P(x,t) \) is the density of the diffusing particles at location \( x \) (in units of \( mm \)) at time \( t \) (in units of \( s \)), \( \frac{\partial^\beta}{\partial t^\beta} \) is the time fractional derivative of order \( \beta \) (\( 0 < \beta \leq 1 \)) in the Caputo sense, \( \frac{\partial^{2\alpha}}{\partial |x|^{2\alpha}} \) is the Riesz space fractional derivative of order \( 2\alpha \) (\( \frac{1}{2} < \alpha \leq 1 \)), \( D_{\alpha,\beta} = D_{1,2} \frac{\tau^{1-\beta}}{\mu^{2(1-\alpha)}} \) is the generalised anomalous diffusion coefficient with units of \( mm^{2\alpha}/t^\beta \), \( D_{1,2} \) in units of \( mm^2/s \) is the diffusion coefficient in the tissue, \( \mu \) and \( \tau \) are the constants for preserving units. The solution of the above fractional diffusion equation (1) in Fourier space is:

\[
p(k,t) = E_\beta\left(-D_{\alpha,\beta}|k|^{2\alpha}t^\beta\right),
\]

(2)

where \( E_\beta(z) = \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(1+\beta n)} \) is the single-parameter Mittag-Leffler function, \( \Gamma \) is the standard Gamma function and by definition \( E_1(z) = \exp(z) \).

In the context of diffusion MRI, \( k \) in Eq. (2) represents the q-space parameter \( q = \gamma G \delta \), \( t \) represents the effective diffusion time \( \bar{\Delta} = \Delta - \frac{\delta}{3} \) and \( p(k,t) \) represents the signal intensity \( S(q,\bar{\Delta}) \), and so Eq. (2) can be used to describe the diffusion signal decay as:

\[
S(q,\bar{\Delta}) = S_0 E_\beta\left(-D_{\alpha,\beta}q^{2\alpha}\bar{\Delta}^\beta\right),
\]

(3)

where \( \gamma, \delta, \Delta \) and \( G \) are defined as the gyromagnetic ratio, diffusion pulse duration and separation between the pulses, and diffusion gradient pulse amplitude. Additionally, \( S_0 \) is the signal when \( G = 0 \).

Defining \( b = q^{2\bar{\Delta}} \) in units of \( s/mm^2 \), Eq. (3) can be expressed in terms of \( b \)-values:

\[
S(b,\bar{\Delta}) = S_0 E_\beta\left(-D_{\alpha,\beta}b^{\alpha}\bar{\Delta}^{\beta-\alpha}\right) = S_0 E_\beta\left(-\left(bD_{app}\right)^{\alpha}\right),
\]

(4)

where
\[ D_{\text{app}} = (D_{\alpha, \beta} \bar{\Delta}^{\beta-a})^\frac{1}{\alpha} = \left( D_{1,2} \frac{\tau^{1-\beta}}{\mu^2(1-\alpha)} \bar{\Delta}^{\beta-a} \right)^\frac{1}{\alpha} \] (5)

is the apparent diffusivity in units of \(mm^2/s\) under the CTRW framework and \(\tau\) in units of \(s\) and \(\mu\) in units of \(mm\) are additional parameters ensuring units of \(D_{\text{app}}\) are preserved. Models that can be described under the CTRW framework include:

i) \(\alpha = \beta = 1\) gives the mono-exponential model (MONO), which is the solution to the classical Bloch-Torrey equation:
\[ S = S_0 \exp(-bD_{\text{MONO}}), \quad D_{\text{MONO}} = D_{1,2}; \] (6)

ii) \(\beta = 1\) and \(\alpha\) is a free parameter results in the super-diffusion model (SUPER) (Bennett et al., 2003; Capuani et al., 2013; Hall and Barrick, 2008; Palombo et al., 2011):
\[ S = S_0 \exp(-(bD_{\text{SUPER}})^\alpha), \quad D_{\text{SUPER}} = \left( D_{1,2} \mu^2 (\alpha-1) \bar{\Delta}^{1-a} \right)^\frac{1}{\alpha}; \] (7)

iii) \(\beta\) is a free parameter and \(\alpha = 1\) is the sub-diffusion model (SUB) (Bueno-Orovio et al., 2016; Capuani et al., 2013; Palombo et al., 2011; Yang et al., 2020):
\[ S = S_0 E\beta (-bD_{\text{SUB}}), \quad D_{\text{SUB}} = D_{1,2} \tau^{1-\beta} \bar{\Delta}^{-1}; \] (8)

iv) \(\beta\) is a free parameter and \(\alpha = \beta\) yields the quasi-diffusion model (QUASI) (Barrick et al., 2020):
\[ S = S_0 E\beta \left( -(bD_{\text{QUASI}}) \right), \quad D_{\text{QUASI}} = \left( D_{1,2} \tau^{1-\beta} \mu^2 (\beta-1) \right)^\beta; \] (9)

v) \(\beta\) and \(\alpha\) are both free parameters leads to the CTRW model (Ingo et al., 2015, 2014; Karaman et al., 2016; Yang et al., 2020; Yu et al., 2018):
\[ S = S_0 E\beta \left( -(bD_{\text{CTRW}}) \right), \quad D_{\text{CTRW}} = \left( D_{1,2} \tau^{1-\beta} \mu^2 (\alpha-1) \bar{\Delta}^{\beta-a} \right)^\frac{1}{\alpha}; \] (10)

vi) the fractional Bloch-Torrey (FBT) model (Magin et al., 2008):
\[ S = S_0 \exp(-(bD_{\text{FBT}})^\alpha), \quad D_{\text{FBT}} = \left( D_{1,2} \mu^2 (\alpha-1) \left( \Delta - \frac{2\alpha-1}{2\alpha+1} \delta \right) / \bar{\Delta}^\alpha \right)^\frac{1}{\alpha}. \] (11)
Parameters $D_{MONO}, D_{SUPER}, D_{SUB}, D_{QUASI}, D_{CTRW}$ and $D_{FBT}$ are model specific apparent diffusivities in units of $mm^2/s$. On careful inspection, we may conclude that the FBT model and SUPER models share similarities, both taking the stretched exponential form, with the difference being a different scaling in the apparent diffusivity. Moreover, none of the apparent diffusivities are a function of the diffusion gradient amplitude $G$, they are only a function of diffusion pulse duration, $\delta$, and pulse separation, $\Delta$.

Whilst all these models were developed independent of each other, it is interesting to realise that they are generalisable within the CTRW framework. We should also point out that these models have been created in view of different assumptions on how $b$ is generated based on changes in $\delta$, $\Delta$ and $G$. Nevertheless, from a purely practical viewpoint, one often considers a standard $b$-value regime, i.e. where $G$ is varied and $\delta$ and $\Delta$ are fixed to obtained different $b$-values.

2.2 Diffusion phase diagram

Parameters of the anomalous diffusion models introduced in the previous section do not have a straightforward interpretation when fitted to the diffusion-weighted MRI signal. For this reason, we provide an explanation based on the previously introduced diffusion phase diagram (Metzler and Klafter, 2000). Since we standardised the models, the value of $\alpha$ (space exponent) is in the range $(0.5, 1]$ and the value of $\beta$ (time exponent) is in the range $(0, 1]$. Figure 1 illustrates the diffusion phase diagram in this standard parameter space, with depictions of how different models behave as a function of $\alpha$ and $\beta$. Overlaid on the plot are regions of sub- ($\beta < \alpha$), super- ($\beta > \alpha$), and quasi-diffusion ($\beta = \alpha$). Whilst it is difficult to place the fractional Bloch-Torrey (FBT) model on this diagram, it is considered to be confined to the super-diffusive region of the diffusion phase diagram.

The CTRW model assumes that the diffusion process governed by Fick’s second law is not constrained by Gaussian probability distribution functions. Instead, random walk jump lengths in time are governed by broad probability distributions, thus leading to infinite characteristic waiting time and jump length variance, and the mean-squared-displacement of random walk, $\langle x^2(t) \rangle$, follows a power law time dependence:

$$\langle x^2(t) \rangle \sim t^{\beta/\alpha}, \quad \frac{1}{2} < \alpha < 1, \quad 0 < \beta < 1.$$  \hspace{1cm} (12)
Figure 1. The diffusion phase diagram illustrated over a standardised domain described by $\alpha$ (space exponent) and $\beta$ (time exponent). Depicted are the action of the various models within this domain. Note, a model is sub-diffusive by nature when $\beta < \alpha$ and super-diffusive when $\beta > \alpha$. The special case of $\beta = \alpha = 1$ is the mono-exponential model, and $\beta = \alpha$ leads to quasi-diffusion. Since the fractional Bloch-Torrey (FBT) model shares similarities with the super-diffusion model (SUPER), it is expected to produce parameter estimates in the super-diffusive region. In principle, parameters of the CTRW model may occupy any position in the $\alpha$-$\beta$ domain. The dashed line provides a hypothetical example when $\beta/\alpha = 0.8$, which is used to illustrate where the CTRW model breaks down when diffusion is interpreted via mean-squared-displacement.

Now it is possible to see that in the case of quasi-diffusion, where $\beta/\alpha = 1$, the mean-squared-displacement grows linearly with time, which is a key feature of standard Brownian motion. In both the case of sub-diffusion ($\beta/\alpha < 1$) and super-diffusion ($\beta/\alpha > 1$), the mean-squared-displacement follows a power law (Metzler and Klafter, 2000). For the CTRW model, wherein $\beta$ and $\alpha$ are both free parameters, the power law governing the mean-squared displacement may be obtained by different values for $\beta$ and $\alpha$. For example, a value of 0.8 for $\beta/\alpha$ can be obtained by setting $\beta = 0.8$ and $\alpha = 1$, or in fact any combination of $\beta$ and $\alpha$ which fall on the dashed line shown in Figure 1. This issue does not present in the super-, sub- and quasi-diffusion models, since only one parameter needs to be obtained.
and the solution should fall uniquely on the $\beta = 1$ line, $\alpha = 1$ line or $\beta/\alpha = 1$ line. Hence, careful consideration should be made towards how uniquely $\beta$ and $\alpha$ are estimated based on the CTRW model.

2.3 Diffusion Kurtosis Imaging

Diffusion kurtosis imaging (DKI) was developed in view of diffusion jump lengths not following standard Brownian motion (Jensen et al., 2005), hence jump lengths are assumed to deviate away from the Gaussian probability distribution function. The notion of kurtosis was used to measure the extent of deviation from Gaussian jump lengths, leading to:

$$
\frac{S}{S_0} = \exp(-b D_{DKI} + \frac{1}{6} b^2 D_{DKI}^2 K_{DKI}),
$$

where $D_{DKI}$ is the apparent diffusion coefficient in units of mm$^2$/s, and $K_{DKI}$ is the parameter defining the level of kurtosis. To our best knowledge, a direct link between the DKI formulation and the sub-diffusion model, provided as Eq. (8), has not been made to date. We propose the estimation of kurtosis from the sub-diffusion model, which overcomes having to limit $b$-values to less than 3000s/mm$^2$, a key requirement of Eq. (13) when fitted to data (Jensen et al., 2005; Jensen and Helpern, 2010).

We will now show how to use the sub-diffusion model to describe kurtosis. Since the parameters in the sub-diffusion model are real and positive, we are dealing with a real-value Mittag-Leffler function. This allows us to take natural logarithm of the sub-diffusion model, Eq. (8), and obtain:

$$
\log(S/S_0) = \log(E_\beta(-bD_{SUB})).
$$

Taking Taylor series expansion at $b = 0$ gives:

$$
\log(E_\beta(-bD_{SUB})) = -\frac{b D_{SUB}}{\Gamma(1+\beta)} + \left(\frac{1}{\Gamma(1+2\beta)} - \frac{1}{2\Gamma(1+\beta)^2}\right) b^2 D_{SUB}^2 + O(b^3).
$$

Letting

$$
D^* = \frac{D_{SUB}}{\Gamma(1+\beta)^\gamma}
$$

leads to the DKI equivalent form:
\[ \log(E_\beta(-bD_{\text{SUB}})) = -bD^* + \frac{1}{6} b^2 D^{*2} K^* + O(b^3), \]  
\text{(17)}

with

\[ K^* = 3 \left( \frac{\Gamma(1+\beta)^2}{\Gamma(1+2\beta)} - 1 \right), \]  
\text{(18)}

where \( 0 < K^* \leq 3 \) for \( 0 < \beta \leq 1 \). Note, when \( \beta = 1 \), the kurtosis \( K^* = 0 \), corresponding to the Gaussian case of diffusion. Hence, according to Eq. (17), the DKI model can be considered as a second order approximation of the sub-diffusion model:

\[ S/S_0 = E_\beta(-bD_{\text{SUB}}) \approx \exp \left( -bD^* + \frac{1}{6} b^2 D^{*2} K^* \right). \]  
\text{(19)}

This link between the DKI model and the sub-diffusion model allows diffusivity \( D^* \) and diffusion kurtosis \( K^* \) to be computed from the sub-diffusion model parameters \( D_{\text{SUB}} \) and \( \beta_{\text{SUB}} \) according to Eqs. (16) and (18), respectively. The relationship between sub-diffusion model and its 1st to 4th order approximations based on Eq. (17) including DKI form is illustrated in Figure 2(a). Since DKI is taking quadratic form (yellow dashed line), to estimate the kurtosis based on DKI formulation, the valid range of \( b \)-value is limited to up to \( b = 3000 \text{s/mm}^2 \). But using the sub-diffusion formulation, no such limitation on \( b \)-value is applied and in fact the kurtosis \( K^* \) can be obtained as a complementary parameter based on \( \beta_{\text{SUB}} \), see Eq.(18), with the relationship illustrated in Figure 2(b). Diffusivity, \( D^* \), can be computed based on \( D_{\text{SUB}} \) and \( \beta_{\text{SUB}} \), see Eq. (16), with the relationship shown in Figure 2(c).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Link between sub-diffusion and DKI models: (a) plot of the natural logarithm of the sub-diffusion model and its approximations according to Eq. (17). MONO and DKI are the first- and second-order approximations of \( E_\beta(-bD_{\text{SUB}}) \). (b) Relationship between \( \beta \)-value and \( K^* \) based on sub-diffusion model and its second-order approximation. (c) Relationship between \( \beta \)-value and \( D^* \) based on sub-diffusion model and its first-order approximation.}
\end{figure}
the sub-diffusion model, respectively; (b) relationship between kurtosis $K^*$ and $\beta_{SUB}$ according to Eq. (18); (c) relationship between the ratio $D^*/D_{SUB}$ and $\beta_{SUB}$ according to Eq. (16). $D^*$ and $K^*$ are the diffusivity and kurtosis computed from sub-diffusion model parameters $D_{SUB}$ and $\beta_{SUB}$.

3 METHODS

We performed a simulation study based on ActiveAX (Alexander et al., 2010), a white matter tissue model, with results provided in Supplementary Information. A key parameter of this simulation model is mean axon radius, and we therefore evaluated how parameters mapped using the different models Eqs. (6-11) vary with changes in axon radii. This simulation indicates anomalous diffusion model parameters are sensitive to the change in axon radii, which is a key observation of white matter microstructure alteration related to normal aging (Stahon et al., 2016). In what follows, we describe the specific data and methods used in this study. We focused on investigating how white matter derived parameters according to the anomalous diffusion models (6)-(11) vary with age in 30 healthy participants between 19 and 67 years of age. The study used high-resolution multiple diffusion-weighting MRI data collected using a 7T human MRI scanner.

3.1 In vivo human diffusion-weighted MRI data

The study was approved by the human ethics committee of the University of Queensland, Brisbane, Australia. We recruited 30 healthy participants aged 19 to 67 years with mostly 2-3 year age gaps and a maximum of a 7 year age gap (37-44), and half of the participants were female. The dMRI data were collected using a 7T Siemens Magnetom research MRI scanner with the following acquisition parameters: TE = 73 ms, TR = 7,244 ms, isotropic resolution of 1.6 mm$^3$, $b = 0, 500 (12 \text{ dirs}), 1500 (24 \text{ dirs}), 2500 (36 \text{ dirs}), 3500 (48 \text{ dirs})$, s/mm$^2$, with $\delta = 21.6 \text{ ms}$ and $\Delta = 31.9 \text{ ms}$. With increasing $b$-value the number of diffusion directions (in parenthesis) were increased. A total of 126 acquisitions including six $b = 0$ measurements were acquired for each participant; gradient directions at each $b$-value were chosen based on the electrostatic model (Jones et al., 1999; Landman et al., 2007). Acquisition of diffusion weighted MRI data took 18 minutes for each participant.
All diffusion-weighted MRI data were denoised using MRtrix (MRtrix 3.0, http://www.mrtrix.org/) (Tournier et al., 2019) and simultaneously corrected for motion and eddy current distortions by co-registration to the \( b = 0 \) image using FSL (version 5.0.11, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (Andersson et al., 2016).

To remove the effect of diffusion anisotropy and to increase SNR, geometrically-averaged diffusion-weighted images (i.e. trace-weighted images) were computed across applied gradient directions for each \( b \)-value, and an example set of images is illustrated in Figure 3.

![Figure 3](image_url)

**Figure 3.** An example set of the trace-weighted axial slice images at different \( b \)-values (in units of \( s/mm^2 \)) for a young healthy male participant.

### 3.2 Corpus callosum segmentation

In each human brain the corpus callosum was segmented manually into seven sub-regions (1 – rostrum, 2 – genu, 3 – rostral body, 4 – anterior midbody, 5 – posterior midbody, 6 – isthmus, 7 – splenium, see Figure 4) based on a standardised template (Witelson, 1989) and by using the MIPAV software (https://mipav.cit.nih.gov) (McAuliffe et al., 2001). Segmentations were converted to binary masks, and then values specific to each region were extracted using MATLAB. The average number of voxels in the mid-sagittal section of corpus callosum was 600±92. The average number of voxels in each subregion were 22±10 in rostrum, 109±33 in genu, 100±19 in rostral body, 68±13 in anterior midbody, 63±15 in posterior midbody, 68±14 in isthmus, and 230±47 in splenium.
Figure 4. Diagram of the corpus callosum outline around the mid-sagittal plane of a human adult, depicting the seven subregions: 1 – rostrum, 2 – genu, 3 – rostral body, 4 – anterior midbody, 5 – posterior midbody, 6 – isthmus, 7 – splenium (according to the template in (Witelson, 1989)).

3.3 Parameter estimation

Data smoothing was not performed prior to estimating anomalous diffusion model parameters. Each of the models in Eqs. (6-11) and Eq. (13) were fitted to the trace-weighted diffusion data in a voxel-by-voxel manner using MATLAB’s lsqcurvefit function and using the trust-region reflective algorithm. For the mono-exponential model, Eq. (6), $D_{MONO}$ was estimated using data with $b$-value from 0 to 1,500 $s/mm^2$. For each anomalous diffusion model Eqs. (7-11), the fitted parameters are the corresponding apparent diffusivities and anomalous diffusion indices $\alpha$ and/or $\beta$. Indices $\alpha$ and $\beta$ were bound in the range $(0.5, 1]$ and $(0, 1]$. Fitted model parameters were not found to be sensitive to the choice of initial values. Other optimisation parameters were left at their default values.

Because of the quadratic form of the DKI formula in Eq. (13), as elucidated in Figure 2(a), we used data with $b=0, 500, 1500, 2500s/mm^2$ for estimating $D_{DKI}$ and $K_{DKI}$.

3.4 Statistical analysis

Using the binary masks created in MIPAV, parameter values for each sub-region of the corpus callosum were extracted and averaged for that sub-region. The MATLAB functions fitlm and predict were used to perform linear regression of ROI mean parameter values and to find the 95% confidence interval as a function of age. The MATLAB functions aoctool (analysis of covariance) and multcompare were used to determine if the rate of change of each parameter against age differed significantly across pairs of subregions.
4 RESULTS

4.1 Anomalous diffusion parameters provide tissue contrast

Figure 5 and 6 illustrate the parameter maps and fitting errors for the various diffusion models in Eqs. (6-11) for a young healthy male participant. All the anomalous diffusion parameters provide contrast between white matter, grey matter and CSF. The fitting errors were computed as the root-mean-square error (RMSE) for each voxel. RMSE were similar across different models with slightly higher errors in the CSF region for the mono-exponential and super-diffusion models.

Figure 5. An example set of anomalous diffusion model parameter maps generated from a young healthy male participant diffusion weighted MRI data. Axial and mid-sagittal views of the maps are presented in panel (a) and (b), respectively. Top row in each panel: Parameters $D_{\text{MONO}}, D_{\text{SUPER}}, D_{\text{SUB}}, D_{\text{QUASI}}, D_{\text{CTRW}}$ are the apparent diffusivities generated by each model (in units of mm$^2$/s). Bottom row in each panel: parameters $\alpha$ and/or $\beta$ are the spatial and temporal anomalous diffusion metrics for each model. Note, maps for $(D_{\text{FBT}}, \alpha_{\text{FBT}})$, not shown here, are the same as $(D_{\text{SUPER}}, \alpha_{\text{SUPER}})$ since they both take the stretched exponential form as explained in section 2.1. Abbreviations: MONO (mono-exponential model), SUPER (super-diffusion model), SUB (sub-diffusion...
model), QUASI (quasi-diffusion model), CTRW (continuous time random walk model), and FBT (fractional Bloch-Torrey equation).

**Figure 6.** Root-mean-squared error (RMSE) maps for the different models, obtained for the same participant as in Figure 5. Top and bottom rows correspond with the axial and mid-sagittal views. Note, error maps for the fractional Bloch-Torrey equation are not shown as they were the same as those for the super-diffusion model. Abbreviations: MONO (mono-exponential model), SUPER (super-diffusion model), SUB (sub-diffusion model), QUASI (quasi-diffusion model), and CTRW (continuous time random walk model).

**Figure 7.** Comparison of diffusivity and kurtosis estimated from (a) the sub-diffusion and (b) DKI models. Top row: axial view; bottom row: mid-sagittal view. $D^*$ and $K^*$ were computed based on the sub-diffusion model parameters $D_{SUB}$ and $\beta_{SUB}$, refer to Eqs. (16) and (18); $D_{DKI}$ and $K_{DKI}$ were estimated based on the DKI model provided as Eq. (13).
4.2 Comparison of kurtosis estimated from sub-diffusion and DKI models

Figure 7 shows diffusivity and kurtosis maps computed using two different approaches. In Figure 7(a), the diffusivity $D^*$ and kurtosis $K^*$ were computed based on the sub-diffusion model parameters $D_{SUB}$ and $\beta_{SUB}$. This way of computing kurtosis does not limit the range of b-values used for the estimation. In Figure 7(b), we provide the diffusivity $D_{DKI}$ and kurtosis $K_{DKI}$ estimated from the standard DKI formulation, see Eq. (13), using a nonlinear least square fitting algorithm as in Jensen et al. (2005) with maximum b-value limited to $2500 \, s/mm^2$. Contrast in the kurtosis map appears markedly improved for $K^*$ in comparison with $K_{DKI}$.

4.3 Age-dependent trend of anomalous diffusion parameters in corpus callosum

The detailed correlation analysis with age for each diffusion parameter in the corpus callosum and its seven subregions has been provided in Figures S3-S15 in supplementary materials. Here, we present a summary of the correlation with age for all the diffusion parameters in Figure 8. In terms of apparent diffusivities, most of the apparent diffusivities estimated from each model showed a significant ($p \leq 0.05$) upward (positive) trend with ageing in the corpus callosum, except $D_{QUASI}$ and $D_{CTRW}$. None of the apparent diffusivities were sensitive to the change of age in the splenium and anterior midbody. All of the anomalous diffusion indices ($\alpha$ and/or $\beta$) show an upward trend with aging in the splenium, except for $\beta_{CTRW}$. No significant trends were found in the anterior midbody, posterior midbody and isthmus subregions for any of the anomalous diffusion indices. The trend with ageing in rostrum, genu and rostral body subregions was not consistent for the anomalous diffusion indices, for example, $\alpha_{SUPER}$ showing downward (negative) correlation in rostral body, $\beta_{QUASI}$ and $\alpha_{CTRW}$ showing no correlation, $\beta_{SUB}$ and $\beta_{CTRW}$ showing upward correlation in genu. The kurtosis $K^*$ computed from subdiffusion model parameters shows downward trend with aging in rostrum, genu and splenium, a finding consistent with the $K_{DKI}$ trend.

In addition, analysis of covariance and pairwise comparison of the slopes of model parameters against age showed no significant differences between the slopes across subregions for each anomalous
diffusion parameter, which may indicate no significant differences in the rate of ageing across the corpus callosum subregions.

**Figure 8.** Summary of the correlation between age and various diffusion model parameters in the corpus callosum and its seven sub-regions (marked with * when $p \leq 0.05$, otherwise $p \leq 0.1$). The correlation coefficient has been colour-coded. Yellow indicates positive correlation, blue indicates negative correlation, and blank indicates correlation is not significant (NS). Abbreviations: MONO (mono-exponential model), SUPER (super-diffusion model), SUB (sub-diffusion model), QUASI (quasi-diffusion model), CTRW (continuous time random walk model), DKI (diffusional kurtosis imaging).

5 DISCUSSION

We have provided equations for the super-diffusion (i.e. stretched exponential), sub-diffusion, quasi-diffusion, CTRW and fractional Bloch-Torrey models within a general framework that allows the different model parameters to be related. In addition, the mathematical link between the sub-diffusion and DKI model parameters was described. We then evaluated how the various anomalous diffusion model parameters varied with age (30 participants, 19-67 years of age) in the human corpus callosum, the primary white matter structure within the brain. Our key findings are as follows: (i) the trends with
age in the various apparent diffusion coefficients, $\alpha$ and $\beta$ were significant in different sub-regions (as summarised in Figure 8), suggesting that these diffusion metrics are sensitive to different age-related tissue microstructural changes in the corpus callosum; (ii) no significant trends were found for any of the anomalous diffusion parameters in the anterior and posterior midbody sub-regions, indicating the midbody regions of the corpus callosum were less age dependent; (iii) the slopes of the trends in the sub-regions exhibited no significant differences, implying rates of ageing across different sub-regions to be consistent; and (iv) $D^*$ and $K^*$ computed from the sub-diffusion model parameters $D_{SUB}$ and $\beta_{SUB}$, without limiting maximum b-value to 3000 s/mm$^2$, provide superior contrast in comparison with those produced based on fitting the traditional DKI model (refer to Figure 7).

### 5.1 Parameter changes with aging

Diffusion tensor imaging metrics obtained in the corpus callosum are not expected to be different due to gender (Francisco Aboitz et al., 1992; Hasan et al., 2005; Ota et al., 2006). In terms of aging, it has been shown that diffusivity increases, whilst fractional anisotropy decreases with age (Barrick et al., 2010; Fenoll et al., 2017; Ota et al., 2006; Pfefferbaum et al., 2000). Given that fractional anisotropy is a measure of how anisotropic diffusion is within white matter fibre bundles, a decrease in this parameter suggests that diffusivity is becoming more isotropic. This can occur due to an increase in axon radius, as the apparent radial diffusivity becomes larger, or can be due to loss of fibre density. An overall increase in diffusivity was in agreement with a decrease in fractional anisotropy, since mean diffusivity is simply the average of the diffusivities in the three principal directions and an increase in any direction leads to an overall increase in diffusivity. Our results also indicated a positive trend with age in corpus callosum in the value of apparent diffusivity derived from various anomalous diffusion models as shown in Figure 8.

White matter structure is known to vary across the corpus callosum sub-regions (F. Aboitz et al., 1992), and anomalous diffusion studies have shown sensitivity to variations in axon radii (Yu et al., 2018, 2017). Moreover, anomalous diffusion model parameters have been suggested to provide complimentary information to diffusion tensor imaging metrics, and may contain information on myelin and iron in tissue (Caporale et al., 2017; Guerreri et al., 2019). We suspect that the additional
information gained is via the spatial anomalous diffusion parameter (\(\alpha\) in our case, and \(\gamma\) in Caporale et al. (2017) and Guerreri et al. (2019)) since there appears to be a clear correlation between the variance shared by radial diffusivity (a change affecting fractional anisotropy) and the spatial anomalous diffusion parameter \(\alpha\). Others have also proposed that the temporal exponent (Palombo et al., 2011), i.e. \(\beta\) in our case, is influenced by the presence of inhomogeneous magnetic fields introduced by spatial variations in tissue microstructure. Further investigations remain needed on the biophysical interpretation of anomalous diffusion model parameters for future work.

Previous study (Guerreri et al., 2019) found that the \(\gamma\)-metric (i.e., \(\alpha\) in our study) from the stretched exponential model (i.e., super-diffusion model) is positively correlated to aging in genu. To our best knowledge, this is the only study to date on the correlation between aging and anomalous diffusion model parameter. Our study investigated age-related changes in five existing anomalous diffusion models including the one in Guerreri et al. (2019), and generalised them under the continuous time random walk framework. Our results showed that age is positively correlated with all the anomalous diffusion parameters in splenium, and \(\beta_{SUB}\) and \(\beta_{CTRW}\) showed positive correlation with age in genu. Although the age ranges were similar between our study and Guerreri et al. (2019), we did not find significant correlation between age and \(\alpha_{SUPER}\) (i.e., the \(\gamma\)-metric) in genu as in Guerreri et al. (2019).

We may attribute the different findings to different diffusion times used (\(\Delta = 107\, ms\) in Guerreri et al. (2019) compared to \(\Delta = 31.9\, ms\) in our study), and different spatial resolutions (in-plane \(1.8 \times 1.8\, mm^2\), slice thickness \(3\, mm\) at 3T in Guerreri et al. (2019) compared to isotropic resolution \(1.6 \times 1.6 \times 1.6\, mm^3\) at 7T in our study).

Our link between \(\beta_{SUB}\) and \(K^*\) is in agreement with previous age-related findings, whereby it was shown that kurtosis decreases with age (Gong et al., 2014; Guerreri et al., 2019), agreeing with the \(K^*\) derived via \(\beta_{SUB}\) from the sub-diffusion model.

5.2 Diffusion Kurtosis Imaging
Using the DKI method outlined in Eq. (13), values for $D_{DKI}$ (apparent diffusivity) and $K_{DKI}$ (kurtosis) are approximated. It has been reported that the estimation of DKI model parameters can be difficult (Rosenkrantz et al., 2015; Szczepankiewicz et al., 2013), primarily because the exponent takes the form:

$$-bD_{DKI} + \frac{1}{6} b^2 K_{DKI} = -bD_{DKI} \left( 1 - \frac{1}{6} bD_{DKI} K_{DKI} \right),$$

where the $1 - \frac{1}{6} bD_{DKI} K_{DKI}$ term essentially multiplies the $-bD_{DKI}$ term. Now, considering the worst-case scenario, i.e. $K = 3$, we obtain:

$$-bD_{DKI} \left( 1 - \frac{1}{2} bD_{DKI} \right),$$

where the factor $bD_{DKI}$ tends to be around 1 in the brain when $b$ is on the order of 1,000 s/mm$^2$ (Yablonskiy and Sukstanskii, 2010). Based on this relationship, and given small b-value data, it is therefore possible to approximate $D_{DKI}$ using the mono-exponential model ($\frac{1}{2} bD_{DKI} < \epsilon$, some finite small number for a sufficiently small $b$). However, the choice of b-values to use in obtaining an approximate for $D_{DKI}$ remains unclear, as the second term is at best of size $\epsilon$, which is likely to be on the order of 0.1. Additionally, the contribution from $1 - \frac{1}{6} bD_{DKI} K_{DKI}$ to the overall value of the exponent depends on the product $D_{DKI} K_{DKI}$, the value of which changes with changes in either $D_{DKI}$ or $K_{DKI}$, or held constant by changing both but in opposite directions. For the latter case, when $D_{DKI} K_{DKI}$ is a fixed value, $D_{DKI}$ is the only factor controlling how well the DKI model fits the data. Here, the fitting is basically mono-exponential by nature, and $K_{DKI}$ is arbitrarily scaled to keep the second part of the term constant.

The challenge of knowing whether there could be an interplay between $D_{DKI}$ and $K_{DKI}$ does not arise in fitting the sub-diffusion model, see Eq. (8), since this problem does not degenerate as multiplication of two unknowns is not a feature of the model.

In addition, since DKI takes a quadratic form (yellow dashed line in Figure 2(a)), to estimate the kurtosis based on DKI formulation, the maximum of b-value is limited to 2000-3000s/mm$^2$ in the brain (Jensen and Helpern, 2010), a value previously reported to be the upper limit for model fitting. However, using
the new link between DKI and the sub-diffusion formulation, a limitation on the maximum b-value does not have to be set. The diffusivity, $D^*$, and kurtosis, $K^*$, can be obtained as complementary parameters based on the sub-diffusion model parameters $D_{SUB}$ and $\beta_{SUB}$. Furthermore, because a limit on b-value does not have to be imposed for fitting, this new approach of computing kurtosis using the full b-value dataset may provide a more accurate measurement of kurtosis, as the spatially resolved $K^*$ map elucidated superior grey-white matter contrast in comparison with the traditional DKI metric (compare $K^*$ and $K_{DKI}$ in Figure 7).

5.3 Time-dependent Diffusion

Time-dependent diffusivity has been described in the context of MRI and in the presence of a complex tissue environment for water diffusion. Various models and concepts have been proposed which account for time-dependence of diffusion (Burcaw et al., 2015; Fieremans et al., 2016; Lee et al., 2020). Whilst our motivation here has not been to map time dependent diffusion, we should nonetheless point out that the most general anomalous diffusion model, the CTRW framework, can provide an explanation of the time dependent diffusivity. From Eq. (5), the diffusivity approximated by fitting the CTRW model is of the form $D_{app}(\tilde{\Delta}) = (D_{a,\beta}\tilde{\Delta}^{\beta-a})^{\frac{1}{\alpha}}$, where $\tilde{\Delta} = \Delta - \delta/3$ is the effective diffusion time, and $D_{a,\beta}$ is the generalised anomalous diffusion coefficient in tissue as defined in section 2.1. Hence, when the effective diffusion time $\tilde{\Delta}$ is changing in the experiment, time dependent diffusivity can be observed. For example, from Figure 5, in white matter, we see that $\alpha_{CTRW}$ is around 0.9 and $\beta_{CTRW}$ is around 0.4, if $\tilde{\Delta}$ is changing then we expect the diffusivity $D_{app}$ is changing with $\tilde{\Delta}^{\beta-a} \approx \tilde{\Delta}^{-0.5}$, i.e., $D_{app}$ is decreasing with increasing diffusion time $\tilde{\Delta}$, as seen in Fieremans et al. (2016).

Our data in this study was generated using a fixed diffusion time imaging protocol. Therefore, we are unable to infer on time dependence of diffusion or how it changes with aging based on anomalous diffusion models evaluated. Nonetheless, it would be an interesting experiment to evaluate the influence of a changing $\tilde{\Delta}$ withing the CTRW framework. Moreover, $\alpha = \beta$ leads to the quasi-diffusion model, where the mean squared displacement grows linearly with time as in the mono-exponential model. Notably, in this case the contribution from $\tilde{\Delta}$ is removed, and appears that for this model the way $b$-
values are set are not expected to impact diffusion time dependence. This conclusion is only observational based on the mathematical expressions presented and should be evaluated experimentally as future work.

6 CONCLUSION

We evaluated how anomalous diffusion model parameters vary as a function of age based on various existing anomalous models. We found that anomalous diffusion model parameters show significant trends with aging in the anterior and posterior sub-regions of corpus callosum, suggesting anomalous diffusion model parameters are sensitive to age-related tissue microstructural changes in corpus callosum. Additionally, the mathematically demonstrated link between the DKI and sub-diffusion models provides a new alternative and explicit way of computing kurtosis and apparent diffusivity, with important advantages that the maximum b-value is not limited to 3000 s/mm². Future work may see the extension of the method to estimating diffusion and kurtosis tensors based on multiple direction diffusion-weighted data. Overall, our results suggest that anomalous diffusion equations play an important role in deriving white matter specific micro-parameters.

ACKNOWLEDGEMENT

Q. Yang thanks the Australian Research Council (ARC) for funding her Discovery Early Career Research Award (DE150101842). V. Vegh acknowledges the National Health and Medical Research Council (NHMRC) for funding a project grant (APP1104933) on tissue microstructure imaging. Q. Yang and V. Vegh also acknowledge the support of the Australian Research Council Discovery Project Award DP190101889. Data for this project was collected using a National Imaging Facility (NIF) 7T human MRI scanner, housed at the Centre for Advanced Imaging, University of Queensland. We thank Surabhi Sood, Aiman Al Najjar and Nicole Atcheson for helping with participant scans.
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**Supplementary Information**

**ActiveAX white matter model**

The ActiveAx model of water diffusion in white matter (Alexander et al., 2010) represents axonal fibres as cylinders having a mean radius, $R$. This model considers four signal compartments, $S_{ia}$, $S_{ea}$, $S_{csf}$ and $S_{tw}$, where $ia$ is intra-axonal (restricted), $ea$ is extra-axonal (hindered), $csf$ is cerebrospinal fluid (free diffusion), and $tw$ is trapped water in between myelin layers (stationary water). The model assumes water molecule exchange is at least an order of magnitude slower than diffusion in any of the four compartments, and therefore it is not modelled. The total diffusion MRI signal is given by

$$S^* = f_{ia}S_{ia} + f_{ea}S_{ea} + f_{csf}S_{csf} + f_{tw}S_{tw},$$

where $f$ represents volume fraction of each compartment with $f_{ia} + f_{ea} + f_{csf} + f_{tw} = 1$. The signal for each compartment is described as:

1. $S_{ia} = S_0^* \exp(-\gamma^2 G^2 \delta^2 R^2)$ represents the signal from intra-axonal water restricted inside parallel cylinders (Vangelderen et al., 1994), where $S_0^*$ is the MR signal with no diffusion weighting, $R$ is the radius of the cylinders, $\gamma$ is the gyromagnetic ratio of water protons, $G$ is the amplitude of the pulsed gradients, and $\delta$ is the duration of the pulsed gradient. Intra-axonal diffusion is unrestricted along the axis of the cylinders. This equation was derived in the narrow pulse regime, that is when $\delta \ll \Delta$, meaning the pulse duration has to be much less than the pulse separation.

2. $S_{ea} = S_0^* \exp(-bD_{eff})$ represents the signal from extra-axonal water outside the cylinders, governed by anisotropic Gaussian distributed displacements. The effective diffusivity $D_{eff} = g^T D g$, $g$ is the gradient direction $g = (g_1, g_2, g_3)^T$, $D$ is the diffusion tensor and computed as $D = (D_\parallel - D_\perp)nn^T + D_\perp I$, $n$ is the unit vector representing the fibre orientation, $D_\parallel$ is the diffusivity in direction $n$, $D_\perp$ is the apparent diffusivity perpendicular to $n$, and $I$ is the three dimensional identity matrix. The parallel diffusivity $D_\parallel$ is the same as the intrinsic diffusivity inside the cylinders in the model for $S_{ia}$. The relationship between $D_\parallel$ and $D_\perp$ was set by a
simple tortuosity model (Szafer et al., 1995) as $D_{\perp} = D_{\parallel}(1 - v)$, where $v = f_{ia}/(f_{ia} + f_{ea})$ assuming CSF and stationary compartments do not contribute to $S_{ea}$.

3. $S_{csf} = S_0^* \exp(-bD_{csf})$ represents the signal from CSF, which is governed by isotropic Gaussian displacements.

4. $S_{tw} = S_0^*$ represents stationary water trapped in subcellular structures such as the gaps between myelin lipid bilayers, which is not attenuated by the diffusion weighting.

To generate simulated DWI data, we set parameters in the ActiveAX model as $D_{\parallel} = 1.7\mu m^2/ms$ (Alexander et al., 2010), $D_{csf} = 3.0\mu m^2/ms$, $f_{ia} = 0.30$, $f_{csf} = 0$, and $f_{tw} = 0.10$, $S_0^* = 1000$, then we derive $f_{ea} = 0.60$, $v = 0.33$, and $D_{\perp} = 1.0\mu m^2/ms$.

Our choice of $f_{ia}$ and $f_{tw}$ resulted in a g-ratio $\frac{R_i}{R_o} = \sqrt{\left(1 + \frac{0.85 + f_{tw}}{0.4 + f_{ia}}\right)^{-1}} = 0.76$ (Thapaliya et al., 2018) where $R_i$ and $R_o$ and inner and outer axon radii, and this value agrees with in vivo human corpus callosum g-ratio estimation, ~0.7 (Berman et al., 2018; Jung et al., 2018). Note that the g-ratio has been shown to be consistent across corpus callosum sub-regions (Thapaliya et al., 2018) and shows little change with age (Berman et al., 2018). We should also point out that it has been shown that an increase in $R$ does not impact $f_{ia}$ and $f_{ea}$ considerably (Kodiweera et al., 2016). We varied $R$ in $S_{ia}$ and investigated how well models were able to fit simulated data.

**Simulation results based on ActiveAx**

Simulated diffusion signal based on the ActiveAX model, shown in Figure S1, suggests that a maximum gradient strength of $0.08 Tm^{-1}$ (same setting for the in vivo dMRI acquisition) is sufficient to distinguish radii between 0.5$\mu m$ and 5$\mu m$ in steps of 0.5$\mu m$. Smaller radii between 0.1$\mu m$ and 0.5$\mu m$ in steps of 0.1$\mu m$ and larger radii between 5$\mu m$ and 10$\mu m$ in steps of 0.5$\mu m$ are more difficult to distinguish from one another. When $D = 1.0\mu m^2/ms$ and $\Delta = 31.9 ms$, a mean displacement $\langle x \rangle = \sqrt{4\Delta D}$ of $\sim 11 \mu m$ is achieved, which is sufficient for boundary restrictions to occur if the maximum $R = 5\mu m$. Furthermore, in Figure S2, fitting the anomalous diffusion models, Eqs.(6)-(11), to the simulated signal shows that anomalous diffusion parameters are sensitive to the changes in axon radius.
Figure S1. Plot of simulated diffusion signal using ActiveAX against b-value. (a) Signal generated for axon radii from 0.1\(\mu m\) to 0.5\(\mu m\) in steps of 0.1\(\mu m\); (b) Signal generated for axon radii from 0.5\(\mu m\) to 5\(\mu m\) in steps of 0.5\(\mu m\); (c) Signal generated for axon radii from 5\(\mu m\) to 10\(\mu m\) in steps of 0.5\(\mu m\).

Figure S2. Scatter plot of anomalous diffusion parameters fitted from ActiveAX data vs axon radius R. Points are color-coded by the size of radius. ActiveAX parameter settings: \(D_\parallel = 1.7\mu m^2/ms, D_\perp = 1.0\mu m^2/ms, D_{csf} = 3.0\mu m^2/ms, f_{ia} = 0.30, f_{ea} = 0.60, f_{csf} = 0, f_{tw} = 0.10,\) and \(S_0^* = 1000.\)
Correlation between anomalous diffusion parameters and age

**Figure S3.** Correlation between age and \( D_{\text{MONO}} \) (in units of \( 10^{-3} \cdot \text{mm}^2/\text{s} \)) from the mono-exponential model within the corpus callosum and its seven subregions. Dots are the mean \( D_{\text{MONO}} \) in each ROI for each participant. Solid lines represent the linear trend between \( D_{\text{MONO}} \) and age. Dashed lines represent the 95% confidence interval. The slope of regression (s in units of \( 10^{-6} \text{mm}^2/\text{s} \cdot \text{year}^{-1} \)), correlation coefficients (r) and the significance level of the linear relationship (p-values) are reported.
Figure S4. Association between age and $D_{SUPER}$ (in units of $10^{-3} \cdot mm^2/s$) from the sub-diffusion model within the corpus callosum and its seven subregions. Dots are the mean $D_{SUPER}$ in each ROI for each participant. Solid lines represent the linear trend between $D_{SUPER}$ and age. Dashed lines represent the 95% confidence interval. The slope of regression (s in units of $10^{-3} \cdot yr^{-1}$), correlation coefficients (r) and the significance level of the linear relationship (p-values) are reported.

Figure S5. Association between age and $\alpha_{SUPER}$ from the super-diffusion model within the corpus callosum and its seven subregions. Dots are the mean $\alpha_{SUPER}$ in each ROI for each participant. Solid lines represent the linear
trend between $\alpha_{SUPER}$ and age. Dashed lines represent the 95% confidence interval. The slope of regression ($s$ in units of $10^{-3} \cdot \text{year}^{-1}$), correlation coefficients ($r$) and the significance level of the linear relationship ($p$-values) are reported.

**Figure S6.** Association between age and $D_{SUB}$ (in units of $10^{-3} \cdot \text{mm}^2/\text{s}$) from the sub-diffusion model within the corpus callosum and its seven subregions. Dots are the mean $D_{SUB}$ in each ROI for each participant. Solid lines represent the linear trend between $D_{SUB}$ and age. Dashed lines represent the 95% confidence interval. The slope of regression ($s$ in units of $10^{-3} \cdot \text{year}^{-1}$), correlation coefficients ($r$) and the significance level of the linear relationship ($p$-values) are reported.
Figure S7. Correlation between age and $\beta_{\text{SUB}}$ from the sub-diffusion model within the corpus callosum and its seven subregions. Dots are the mean $\beta_{\text{SUB}}$ in each ROI for each participant. Solid lines represent the linear trend between $\beta_{\text{SUB}}$ and age. Dashed lines represent the 95% confidence interval. The slope of the regression (s in units of $10^{-3} \cdot \text{year}^{-1}$), correlation coefficients (r) and the significance level of the linear relationship (p-values) are reported.

Figure S8. Association between age and $D_{\text{QUASI}}$ (in units of $10^{-3} \cdot \text{mm}^2/\text{s}$) from the sub-diffusion model within the corpus callosum and its seven subregions. Dots are the mean $D_{\text{QUASI}}$ in each ROI for each participant. Solid
lines represent the linear trend between $D_{QUASI}$ and age. Dashed lines represent the 95% confidence interval. The slope of regression ($s$ in units of $10^{-3} \cdot \text{year}^{-1}$), correlation coefficients ($r$) and the significance level of the linear relationship ($p$-values) are reported.

Figure S9. Correlation between age and $\beta_{QUASI}$ from the quasi-diffusion model within the corpus callosum and its seven subregions. Dots are the mean $\beta_{QUASI}$ in each ROI for each participant. Solid lines represent the linear trend between $\beta_{QUASI}$ and age. Dashed lines represent the 95% confidence interval. The slope of regression ($s$ in units of $10^{-3} \cdot \text{year}^{-1}$), correlation coefficients ($r$) and the significance level of the linear relationship ($p$-values) are reported.
Figure S10. Association between age and $D_{CTRW}$ (in units of $10^{-3} \cdot mm^2/s$) from the sub-diffusion model within the corpus callosum and its seven subregions. Dots are the mean $D_{CTRW}$ in each ROI for each participant. Solid lines represent the linear trend between $D_{CTRW}$ and age. Dashed lines represent the 95% confidence interval. The slope of regression (s in units of $10^{-3} \cdot year^{-1}$), correlation coefficients (r) and the significance level of the linear relationship (p-values) are reported.

Figure S11. Association between age and $\alpha_{CTRW}$ and $\beta_{CTRW}$ from the continuous time random walk (CTRW) model within the corpus callosum and its seven subregions. Purple and green dots are the mean $\alpha_{CTRW}$ and $\beta_{CTRW}$
in each ROI, respectively, for each participant. Solid lines represent the linear trend between $\alpha_{CTR\text{W}}$ and $\beta_{CTR\text{W}}$ and age. Dashed lines represent the 95% confidence interval. The slope of regression (s in units of $10^{-3} \cdot \text{year}^{-1}$), correlation coefficients (r) and the significance level of the linear relationship (p-values) are reported. The two values in each measurement are for $\alpha_{CTR\text{W}}$ and $\beta_{CTR\text{W}}$, respectively.

**Figure S12.** Association between age and $D^*$ (in units of $10^{-3} \cdot \text{mm}^2/\text{s}$) computed based on the sub-diffusion model parameters (refer to Eq.(16)) within the corpus callosum and its seven subregions. Dots are the mean $D^*$ in each ROI for each participant. Solid lines represent the linear trend between $D^*$ and age. Dashed lines represent the 95% confidence interval. The slope of regression (s in units of $10^{-3} \cdot \text{year}^{-1}$), correlation coefficients (r) and the significance level of the linear relationship (p-values) are reported.
Figure S13. Association between age and $K^*$ computed based on the sub-diffusion model parameter (refer to Eq.(18)) within the corpus callosum and its seven subregions. Dots are the mean $K^*$ in each ROI for each participant. Solid lines represent the linear trend between $K^*$ and age. Dashed lines represent the 95% confidence interval. The slope of regression (s in units of $10^{-3} \cdot year^{-1}$), correlation coefficients (r) and the significance level of the linear relationship (p-values) are reported.

Figure S14. Association between age and $D_{DKI}$ (in units of $10^{-3} \cdot mm^2/s$) computed based on the sub-diffusion model parameters (refer to Eq.(16)) within the corpus callosum and its seven subregions. Dots are the mean $D_{DKI}$
in each ROI for each participant. Solid lines represent the linear trend between $D_{DKI}$ and age. Dashed lines represent the 95% confidence interval. The slope of regression (s in units of $10^{-3} \cdot \text{year}^{-1}$), correlation coefficients (r) and the significance level of the linear relationship (p-values) are reported.

**Figure S15.** Association between age and $K_{DKI}$ computed based on the sub-diffusion model parameter (refer to Eq.(18)) within the corpus callosum and its seven subregions. Dots are the mean $K_{DKI}$ in each ROI for each participant. Solid lines represent the linear trend between $K_{DKI}$ and age. Dashed lines represent the 95% confidence interval. The slope of regression (s in units of $10^{-3} \cdot \text{year}^{-1}$), correlation coefficients (r) and the significance level of the linear relationship (p-values) are reported.