Title: Age-related microstructural and physiological changes in normal brain measured by MRI γ-metrics derived from anomalous diffusion signal representation

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Abstract: Nowadays, increasing longevity associated with declining cerebral nervous system functions, suggests the need for continued development of new imaging contrast mechanisms to support the differential diagnosis of age-related decline.
In our previous papers, we developed a new imaging contrast metrics derived from anomalous diffusion signal representation and obtained from diffusion-weighted (DW) data collected by varying diffusion gradient strengths. Recently, we highlighted that the new metrics, named γ-metrics, depended on the local inhomogeneity due to differences in magnetic susceptibility between tissues and diffusion compartments in young healthy subjects, thus providing information about myelin orientation and iron content within cerebral regions. The major structural modifications occurring in brain aging are myelinated fibers damage in nerve fibers and iron accumulation in gray matter nuclei. Therefore, we investigated the potential of γ-metrics in relation to other conventional diffusion metrics such as DTI, DKI and NODDI in detecting age-related structural changes in white matter (WM) and subcortical gray matter (scGM). DW-images were acquired in 32 healthy subjects, adults and elderly (age range 20 to 77 years) using 3.0T and 12 b-values up to 5000s/mm^2. Association between diffusion metrics and subjects' age was assessed using linear regression. A decline in mean γ (Mγ) in the scGM and a complementary increase in radial γ (γ⊥) in frontal WM, genu of corpus callosum and anterior corona radiata with advancing age were found. We suggest that the increase in γ⊥ may reflect declined myelin density, and Mγ decrease may mirror iron accumulation. An increase in D// and a decrease in the orientation dispersion index (ODI) were associated with axonal loss in the pyramidal tracts, while their inverted trends within the thalamus were thought to be linked to reduced architectural complexity of nerve fibers. γ-metrics together with conventional diffusion-metrics can more comprehensively characterize the complex mechanisms underlining age-related changes than conventional diffusion techniques alone.

1   **Age-related microstructural and physiological changes in normal brain measured by MRI γ-**
2   **metrics derived from anomalous diffusion signal representation**

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Highlights

γ metrics provides complementary information compared to conventional diffusion metrics

This study shows the added value of γ-metrics to assess brain alterations due to aging

Axial γ increases in white matter may reflect breakdown of myelin and axonal damage

Mean γ decrease in subcortical gray matter may mirror iron deposit accumulation.

Abstract

Nowadays, increasing longevity associated with declining cerebral nervous system functions, suggests the need for continued development of new imaging contrast mechanisms to support the differential diagnosis of age-related decline.

In our previous papers, we developed a new imaging contrast metrics derived from anomalous diffusion signal representation and obtained from diffusion-weighted (DW) data collected by varying diffusion gradient strengths. Recently, we highlighted that the new metrics, named γ-metrics, depended on the local inhomogeneity due to differences in magnetic susceptibility between tissues and diffusion compartments in young healthy subjects, thus providing information about myelin orientation and iron content within cerebral regions. The major structural modifications occurring in brain aging are myelinated fibers damage in nerve fibers and iron accumulation in gray matter nuclei. Therefore, we investigated the potential of γ-metrics in relation to other conventional diffusion metrics such as DTI, DKI and NODDI in detecting age-related structural changes in white matter (WM) and subcortical gray matter (scGM). DW-images were acquired in 32 healthy subjects, adults and elderly (age range 20 to 77 years) using 3.0T and 12 b-values up to $5000 s/mm^2$. Association between diffusion metrics and subjects' age was assessed using linear regression. A decline in mean γ (Mγ) in the scGM and a complementary increase in radial γ ($\gamma_\perp$) in frontal WM, genu of corpus callosum and anterior corona radiata with advancing age were found. We suggest that the increase in γ⊥ may reflect declined myelin density, and Mγ decrease may mirror iron accumulation. An increase in $D_{//}$ and a decrease in the orientation dispersion index (ODI) were associated with axonal loss in the pyramidal tracts, while their inverted trends within the thalamus were thought to be linked to reduced architectural complexity of nerve fibers. γ-metrics together with conventional diffusion-metrics can more comprehensively characterize the complex mechanisms underlining age-related changes than conventional diffusion techniques alone.

70   **1   Introduction**

71   The human brain undergoes regional-specific structural and physiological changes during lifespan,

72   which are reflected in a decline in cognitive abilities that become less and less efficient with aging

73   (Lockhart et al., 2014). Axonal damage and disintegration, loss of neuronal cells, myelin

74   degradation and iron accumulation (Draganski et al., 2011, Xu et al., 2008, Ashraf et al., 2018) are

75   the main age-related modifications that inexorably occur in the aging brain. With increasing life

76   expectancy in developed countries, there is a great need to establish efficient protocols for the early

77   diagnosis of cerebral decline that can support the development of new drugs and new therapies for

78   both normal and pathological aging.

79   In the last decades, magnetic resonance diffusion imaging (MRI) techniques and in particular

80   diffusion tensor imaging (DTI) studies (Basser et al., 1994) have contributed to the neuroscience of

81   normal ageing and to characterizing changes in morphology and tissues that occur with advancing

82   age. From the fourth decade of life, DTI metrics highlight a decline in fractional anisotropy (FA)

83   and a complementary increase in mean diffusivity (MD) in cerebral white matter (WM) due to

84   aging (Salat et al., 2005). This behavior of the DTI parameters reflects loss of WM fibers and of

85   their directionality and a reduction in axonal diameters (Bartzokis et al., 2012, Callaghan et al.,

86   2014). On the other hand, DTI investigations into cerebral gray matter (GM) as a function of

87   subjects' age, showed less clear patterns (Rathi et al., 2014, Salminen et al., 2016), whereas T1, T2

88   and T2* weighted imaging and susceptibility-based imaging studies highlighted GM atrophy

89   together with an increase in iron content in specific GM regions (Pfefferbaum et al., 2010, Haacke

90   et al., 2010, Daugherty and Raz, 2015, Pirpamer et al., 2016). DTI parameters quantify the diffusive

91   properties of bulk water poorly interacting with the complex structure of the neural tissue, so DTI

92   metrics have a limited sensitivity and specificity in the detection of early microstructural changes in

93   WM and GM. Moreover, the evaluation of early physiological modification due to different iron

94   content in vivo is challenging and still requires further investigation (Pfefferbaum et al., 2010). As a

95   consequence, in the last few years, several methods have been developed to increase the potential

96   ability of MRI diffusion techniques in detecting rearrangement of WM and its modification due to

97   normal and pathological aging, each with its strengths and weaknesses (Jelescu and Budde, 2017).

98   Two complementary approaches have emerged for extracting information on the tissue

99   microstructure exploiting the biological water diffusion signal: signal representation and

100   biophysical tissue modeling (Jelescu and Budde, 2017; Novikov et al. 2018). On the one hand,

101   signal representation or "statistical models" such as DTI and diffusion kurtosis imaging (DKI)

102   quantify parameters deriving from statistical mechanics without assumptions about the underlying

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tissue, but they lack specificity, and provide only an indirect characterization of the microstructure (Kiselev, 2017). On the other hand, biophysical tissue models such as neurite orientation distribution and density imaging (NODDI) require schematic-geometric assumptions about the underlying tissues. Therefore, even if such models can potentially provide greater specificity and interpretation of biologically relevant parameters, the results are dramatically dependent on the initial geometric assumptions that in general may not well describe the main components of tissue microstructures, especially their changes due to pathologies (Novikov et al., 2018). Since DKI is sensitive to water molecules which interact more with the cerebral microstructures than those of bulk water considered in DTI, Kurtosis techniques have been used to study healthy aging as an extension of DTI as these techniques are more sensitive to microstructural changes (Coutu et al. 2014; Gong et al. 2014; Lätt et al. 2013).

In parallel, several strategies have been developed to quantify the differences in magnetic susceptibility ($\Delta\chi$) in brain tissues that potentially offer the possibility to measure the presence of heavy metals, such as iron in GM and WM, and to highlight the directionality, the micro-architecture and the chemical arrangement of the neural tissues. As an example, quantitative susceptibility mapping (QSM) allows the calculation of bulk magnetic susceptibility distribution of tissues in vivo from gradient echo (GRE) magnetic resonance phase images (Langkammer et al., 2012) while susceptibility tensor imaging (STI) quantifies the amount of $\Delta\chi$ anisotropy (Liu, 2010). However, in order to compute the susceptibility tensor, it is necessary to acquire the signal along at least six different orientations of the sample with respect to the static magnetic field (B_0) (Liu, 2010). This is an intrinsic limitation of STI imaging, since subject rotation during acquisition is hardly practicable in clinical applications.

Recently, we showed the potential of the new γ-metrics derived from anomalous diffusion (AD) signal representation in highlighting $\Delta\chi$ in myelin orientation and iron contents within selected regions of WM and subcortical GM (scGM), respectively (Caporale et al., 2017). Because the pseudo-superdiffusion γ parameter depends on the local $\Delta\chi$ at the interface between different tissues and on the distribution and dimension of the diffusion compartments, the γ-metrics could be useful for extracting information complementary to that of the DTI in normal aging studies of the human brain.

Starting from the representation of the diffusion weighted (DW) signal in terms of fractional derivatives (Lin, 2015; Lin 2016; Lin 2018), we quantified the γ parameters using the signal, S(b), obtained with a pulse field gradient (PFG) sequence collected by changing diffusion gradient (g_{diff}) strength at a constant value of the diffusion time Δ. In this framework, DW signal must be fitted to

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137 the stretched exponential function: $S(b) = S(0)exp(-(bD)^{\gamma})$ (Magin et al. 2008, De Santis et al.

138 2011, Hall and Barrick 2012, Ingo et al. 2014). In the context of the transient anomalous diffusion

139 theory, based on the Continuous time random walk (CTRW) (Metzler and Klafter 2000), the γ

140 parameter extracted by fitting the above function to DW data, quantifies superdiffusion processes.

141 Clearly, there is no superdiffusion of water in brain tissues, but the signal representation that we use

142 to quantify γ reflects the additional effect of the magnetization phasing and dephasing due to

143 internal gradients (g_{int}) generated by $\Delta\chi$ at the interface between different tissues. As explained in

144 our previous papers describing in vitro and ex vivo experiments to validate the γ-metrics (Palombo

145 et al. 2011; Palombo et al 2012; Capuani et al. 2013), an ensemble of spins in a voxel can contribute

146 to a further decrease in the DW signal attenuation, when $\mathbf{g}_{int}$ and $\mathbf{g}_{diff}$ are in the same order of

147 magnitude; other spins (that can be located in a voxel far from the first ones) can acquire a phase

148 that will help to increase the signal. Due to indistinguishable spins associated with water molecules,

149 this scenario mimics a super-diffusion regime where water molecules seem to perform longer jumps

150 because their signal disappear in one spot, while appearing instantaneously in another spot. For this

151 reason, we named γ the pseudo-superdiffusion parameter of transient anomalous diffusion. The

152 adjective "transient" means that over a sufficiently long time, diffusion asymptotically becomes

153 normal (or Gaussian) showing a finite asymptotic diffusion value (percolation limit). In this paper,

154 the potential of γ-metrics in detecting WM and scGM changes due to aging is shown regardless of

155 the debate concerning the existence of transient anomalous diffusion in brain tissues (Nicholson,

156 2015; Saxton, 2008; Destainville et al., 2008), as this issue is outside the scope of this study.

157 Towards this goal, γ-metric results in WM and scGM were compared to DTI parameters, mean

158 kurtosis (MK) derived from DKI metrics (Jensen et al. 2010) and NODDI derived parameters

159 (Zhang et al., 2012). Association between diffusion metrics and subjects' age was assessed *via*

160 linear regression. We tested the hypothesis whereby γ-metrics are sensitive to physiological and

161 structural variations that occur in the human brain during aging, such as iron deposition and myelin

162 degradation.

163

2　Materials and Methods

2.1　Studied population

166 A total of 35 volunteers took part in this study after providing informed written consent in

167 compliance with the national laws and with the local ethics committee guidelines. None in the

168 cohort had a history of stroke, head injuries, medical illness or diagnosis of neurological and

169 psychiatric disorders. Of the 35 volunteers, 32 were retained for this study, 19 men and 13 women

170 (age range 20-77 years, Mean+/-SD = 43.7+/-18.2y). One of the volunteers was excluded due to the

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171   presence of brain abnormalities. The other two subjects were discarded because of incomplete data

172   acquisitions and substantial bulk motion.

173   **2.2   Data Acquisition**

174   All volunteers underwent MRI examination using a 3.0T Siemens Magnetom Allegra (Siemens

175   Medical Solutions, Erlangen, Germany) equipped with a circularly polarized transmit-receive coil.

176   The maximum gradient strength was 40 mT/m with a maximum slew rate of 400 T/m/s. The same

177   MRI protocol was applied to all subjects, including whole-brain T1-weighted images and Diffusion-

178   Weighted Spin Echo-Echo Planar Imaging (DW SE-EPI). Care was taken to center each subject's

179   head in the head coil and to restrain subject's motion with cushions and medical tape.

180   Diffusion experiments were performed with the following parameters: $TR/TE = 6400/107$ ms; $\Delta/\delta =$

181     $107/35$ ms; bandwidth = 1860 Hz/px; matrix size = 128×128, number of axial slices= 32; in-plane

182   resolution= 1.8×1.8 mm^2; slice thickness = 3 mm; number of averaged scans NS = 2. The

183   diffusion-encoding gradients were applied along 15 non-collinear directions spanning the entire

184   sphere to minimize the effect of cross-terms between the diffusion gradients and the imaging

185   gradients in the estimation of diffusion parameters (Kingsley, 2006). The set of 15 diffusion

186   directions was chosen among the optimized schemes suggested by Landman et al. being one of the

187   possible minimum potential energy partitions of the scheme of 30 directions proposed by Jones et

188   al., based on the electrostatic repulsion algorithm (Landman et al., 2007, Jones et al., 1999). By

189   varying the gradient strength **g**, 11 different b-values were acquired (b= *200, 400, 600, 800, 1000,*

190   *1500, 2000, 2500, 3000, 4000, 5000* s/mm^2), plus the b0 image with no diffusion weighting, with an

191   anterior-posterior phase encoding direction for all the scans. The acquisition time for the entire

192   diffusion protocol was approximately 37 minutes per subject.

193   **2.3   Data analysis**

194   Figure 1 illustrates the main steps of the image processing pipeline used in this study. After the raw

195   data quality check, all diffusion images were pre-processed to correct for noise effects, Gibbs

196   ringing artifacts, eddy currents and subject's movements. DTI, DKI, NODDI and γ-imaging

197   representative functions (see paragraph 2.4) were fitted to different subsets of the diffusion data. A

198   population-based template was constructed, and all images were co-registered to this template. The

199   analysis was finally carried out using both a ROI-based and a voxel-wise based approach.

200   **2.3.1   Pre-processing**

201   All diffusion images were first visually inspected to check for data quality. Datasets with

202   considerable bulk motion artifacts were discarded.

203   To reduce the noise effect on the diffusion parameter estimation, the MRtrix3 *dwidenoise* tool

204   (Copyright   ©   2016   New   York   University,   University   of   Antwerp,

https://github.com/MRtrix3/mrtrix3) was applied as the first step of the preprocessing (Tournier et al., 2012, Veraart et al., 2016a, Veraart et al., 2016b). Then, the Gibbs ringing correction framework of *Kellner et al* (Kellner et al., 2016) was applied for EPI distortion correction. Finally, the image distortions induced by head motion and eddy currents were corrected using the FSL eddy tool (FMRIB Software Library v5.0, FMRIB, Oxford, UK) (Yamada et al., 2014, Andresson and Sotiropoulos, 2016).

Volunteers: 32 subjects (Age range 20-77y Mean/SD = 44/18y)

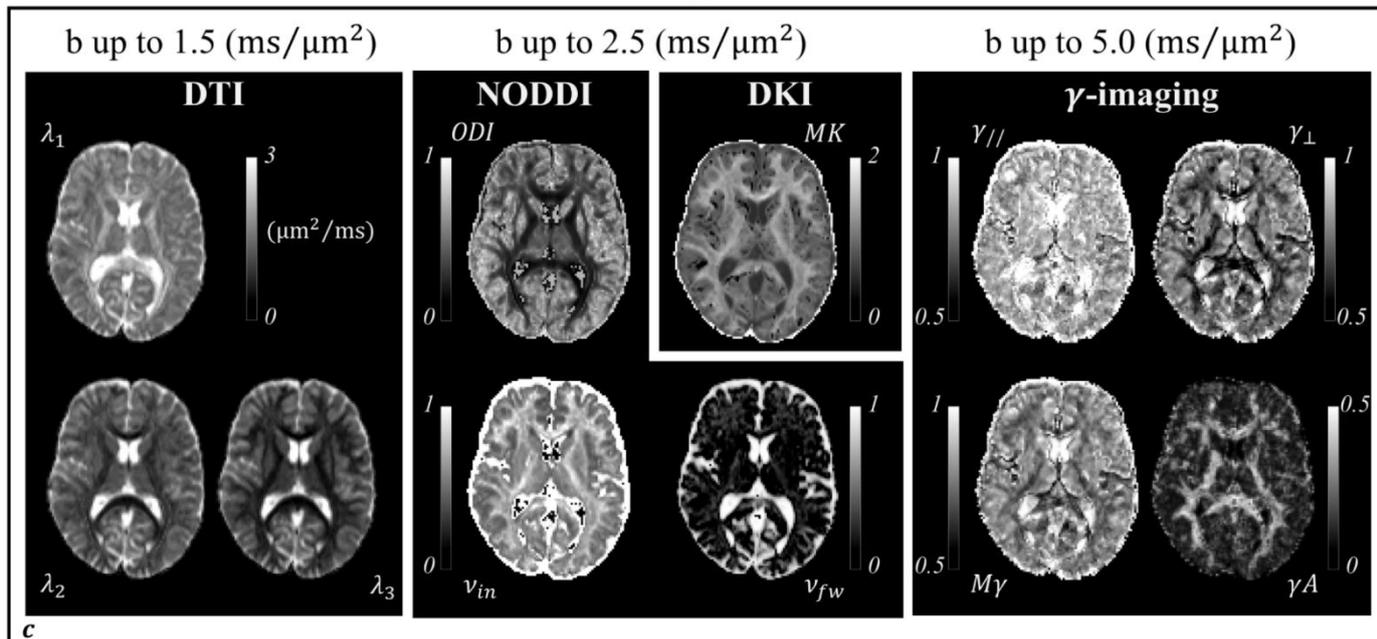Acquisition scheme: 11 b-shells with 15 directions each + b_0

a

Noise correction (Dwidenoise-MRtrix3)

Gibbs ringing correction (Kellner *et al.*)

Eddy current correction (EDDY-FSL)

b

b up to 1.5 (ms/μm²)   b up to 2.5 (ms/μm²)   b up to 5.0 (ms/μm²)

DTI   NODDI   DKI γ-imaging

λ_1 ODI   MK $\gamma_{//}$ $\gamma_\perp$

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(μm²/ms)

0

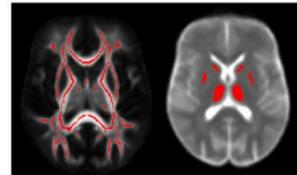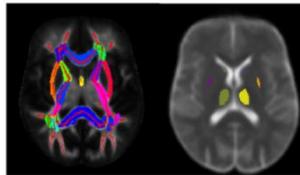λ_2 λ_3 ν_{in} ν_{fw} $M\gamma$ γA

c

Spatial normalization (DTI-TK) + mean FA skeleton (TBSS)

Normalization and projection of the other parametric maps

ROI-based analysis   Voxel-wise analysis

d

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Figure 1: Pipeline of the data processing: the main steps carried out to analyze the diffusion weighted images are schematically summarized. *a*) Brief description of the subjects' cohort and acquisition protocol. *b*) The collected data were then corrected for random noise effects, Gibbs ringing artifacts, movements and eddy current induced artifacts. *c*) Different subsets of the data were used to obtain the different diffusion metrics. *d*) The DT-eigenvalues were used to obtain a population specific template; all the other metrics were then projected onto this template. Associations between subjects' age and diffusion metrics were assessed averaging over regions of interest (ROIs) or voxel-wise.

2.4   Diffusion metrics generation

Different subsets of the pre-processed data were used to compute DTI, DKI, NOODI and γ-imaging diffusion metrics.

2.4.1   DTI and DKI

The cumulant expansion of the log-transformed diffusion weighted signal in powers of b is the most widespread signal representation. By truncating the expansion at the second order in b, the following expression in tensorial form can be obtained (Basser et al., 1994, Jensen et al. 2005):

$$\ln\frac{S(b,g)}{S_0} = -b\sum_{i,j=1}^{3} g_i g_j D_{ij} + \frac{1}{6}b^2\left(\sum_{i=1}^{3}\frac{D_{ii}}{3}\right)\sum_{i,j,k,l=1}^{3} g_i g_j g_l g_k W_{ijkl} \tag{1}$$

Here g is the direction of the applied diffusion weighting, D is the rank-2 diffusion tensor and W is the rank-3 kurtosis tensor. For moderate b-values, the above expression can be truncated at the first order, recovering the conventional diffusion tensor imaging (DTI) (Basser et al., 1994).

In this study, DTI analysis was performed *via* FSL dtifit tool, considering the b-shells between $b = 200$ and $b = 1500$ s/mm^2 (i.e. 6 b-values). The dtifit routine returns MD and FA maps together with the three diffusion tensor eigenvalues (λ_1, λ_2, λ_3, with $\lambda_1 > \lambda_2 > \lambda_3$) and eigenvectors ($V_1$, V_2, V_3), which define the DTI reference frame (DTI-rf) voxel-wise. The axial (D//) and radial (D⊥), diffusivities were computed as follows: D//= λ_1, D⊥=(λ_2+λ_3)/2.

By fitting equation (1) to the logarithm of the signal, having acquired at least 21 measures distributed over two b-shells, it is possible to reconstruct the kurtosis tensor W (Jensen et al. 2005). Diffusion kurtosis imaging (DKI) is a clinically feasible extension of DTI at higher b-values that probes restricted water diffusion in tissues providing information about the tissue complexity. In this work, we used the b-shells up to the b = 2500 s/mm^2 to get mean kurtosis (MK) weighted maps. In order to obtain these maps we used the dki_lls method from the *md-dmri* software (*https://github.com/markus-nilsson/md-dmri/tree/master/methods*). After obtaining the W tensor components, MK was calculated voxel-wise as the average of W elements across the sphere, in a fast and robust way (Hansen et al., 2013).

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2.4.2 NODDI

The NODDI model function (Zhang et al., 2012) was fitted to all the b-shells up to $b = 2500$ s/mm^2, using the toolbox available online (https://www.nitrc.org/projects/noddi_toolbox). NODDI is a biophysical tissue model for DW data that aims to infer specific information about the tissue micro-structure. The normalized total diffusion signal, A, is expressed as the sum of contributions from different comportments:

$$A = \left(1 - v_{fw}\right)\left[\left(1 - v_{in}\right)A_{en} + v_{in}A_{in}\right] + v_{fw}A_{fw}, \qquad (2)$$

where A_{in} and v_{in} represent the intra-neurite normalized signal and volume fraction, A_{en} is the extra-neurite normalized signal and A_{fw} and v_{fw} represent the normalized signal and volume fraction of the compartment modeling isotropic free-water contributions to the signal (such as CSF). Fitting NODDI to DW-data makes it possible to obtain an estimate of v_{in} and v_{fw}, with values comprised between 0 and 1. Moreover, NODDI quantifies the so-called orientation dispersion index (ODI) that attempts to estimate the orientation dispersion of the neurites within each voxel. ODI values run from 0, referring to an isotropically oriented distribution, to 1, referring to a perfectly coherent bundle of fibers.

2.4.3 γ-imaging

Several theoretical models have been proposed to describe anomalous diffusion phenomena, such as the (CTRW) model (Metzler and Klafter 2000), the fractional motion (FM) model and others (Metzler et al. 2014). The adaptation of these models to MRI diffusion experiments, permits fitting of experimental DW data to functions containing stretched exponentials and others derived parameters (Magin et al. 2008; Zhou et al. 2010; Ingo et al. 2014; Caporale et al. 2017; Yu et al. 2018; Karaman and Zhou 2018). Unfortunately, different authors have assigned different nomenclatures to indicate the same parameter, fueling the confusion that characterizes the literature of anomalous diffusion methods in MRI.

Recently, two anomalous diffusion parameters were introduced in NMR: α and γ. α quantifies sub-diffusive processes and it is measured by varying diffusion time Δ in a pulse field gradient (PFG) MRI sequence. Conversely, γ quantifies super-diffusive processes characterized by a divergence of the jump length variance, and it is measured by varying gradient strengths g in a PFG sequence at a fixed value of Δ (Palombo et al.2011; Capuani et al. 2013). In the present work, diffusion experiments by varying g at a fixed value of Δ were performed. Therefore, super-diffusive processes were quantified. Clearly, no real super-diffusive processes of water in biological tissues exist, but "pseudo-superdiffusion" processes mainly due to a local background gradient derived from $\Delta\chi$ at the interface between different diffusion

281   compartments and to the different diffusion lengths with which the water molecules diffuse in several

282   compartments.

283   As the diffusion weighted NMR signal is proportional to the Fourier transform (FT) of the motion

284   propagator (MP), for investigating pseudo-superdiffusive processes it is possible to use the

285   following function (Metzler and Klafter 2000) as FT of the anomalous diffusion MP:

286 $$W(q, t) \simeq \exp\left[- K_{2\gamma} |2\pi q|^{2\gamma} \Delta\right] \tag{3}$$

287

288   where $K_{2\gamma}$ is a generalized diffusion constant, whose units are $(ms^{-1})^{2\gamma}$ with $q=1/(2\pi)\Gamma g\delta$ the wave vector

289   and $0 <\gamma< 1$. For a fixed value of Δ, the stretched exponential form of signal attenuation as a function of b

290   value can easily be derived from (3). Indeed, by replacing $|2\pi q|^{2\gamma} = b^\gamma/\Delta^\gamma$ in (3), the following relations can

291   be obtained:

292

293 $$\frac{S(b)}{S(0)} \simeq \exp\left[\frac{K_{2\gamma}}{\Delta^{(\gamma-1)}} b^\gamma\right] = \exp\left[\frac{D\,\rho^{2(\gamma-1)}}{\Delta^{(\gamma-1)}} b^\gamma\right] = \exp\left[- (D_{eff}b)^\gamma\right] \tag{4}$$

294

295   where D is the diffusion coefficient, $\rho^{2(\gamma-1)}$ and $\Delta^{(\gamma-1)}$ are fractional order space and time constants

296   that preserve units, and D_{eff} is a generalized effective diffusion constant.

297   All the b-shells were used for γ-imaging analysis. To obtain the γ metrics, a custom-made Matlab

298   script (MATLAB R2016b) was used. Specifically, the approach described by *Caporale et al.*,

299   (Caporale et al., 2017) was used in which the reference frame of the tensor representing the transient

300   anomalous diffusion was assumed to coincide with that of the DTI (DTI-rf) (De Santis et al., 2011,

301   Caporale et al., 2017). The choice of projecting the stretched γ-exponents along the axes of DTI-rf

302   assumes that, to a first approximation, anomalous and normal (i.e. Gaussian) diffusion share the

303   same rotationally invariant reference frame (De Santis et al. 2011). The resulting signal

304   representation showing transient anomalous pseudo-superdiffusion is written as:

305

306 $$\frac{S(b)_j}{S(0)} = e^{- \sum_{i=1}^{3} A_i \left(b(V_i \cdot g_j)\right)^{\gamma_i}} \tag{5}$$

307

308   Here j denotes the diffusion direction defined by the gradient vector g_j; *i* indicates each of the 3

309   main axes with respect to a diffusive motion along a generic direction which may be decomposed; γ_i

310   and A_i are, respectively, the anomalous diffusion exponents and the generalized diffusion

311   coefficients estimated along the direction identified by the eigenvector V_i in the DTI-rf.

312   The estimated γ-exponents $\gamma_1, \gamma_2, \gamma_3$ (with $\gamma_1 > \gamma_2 > \gamma_3$) are adimensional parameters that take

313   values from 0 to 1. γ_i equal to 1 indicates a normal Gaussian diffusion, while values of $\gamma_i < 1$

314   indicate a departure from Gaussian diffusion.   The following γ-metrics were finally computed:

315   axial-γ ($\gamma_{//} = \gamma_1$), radial-γ ($\gamma_\perp = \frac{\gamma_2 + \gamma_3}{2}$), mean-γ ($M\gamma = \frac{\gamma_1 + \gamma_2 + \gamma_3}{3}$), γ-anisotropy ($\gamma A =$

316    $\sqrt{\frac{3\left[(\gamma_1 - M_\gamma)^2 + (\gamma_2 - M_\gamma)^2 + (\gamma_3 - M_\gamma)^2\right]}{2(\gamma_1{}^2 + \gamma_2{}^2 + \gamma_3{}^2)}}$). Specifically, γ// represented the projection of the anomalous

317   exponent in the direction described by the first eigenvector $\mathbf{V}_1$ of the Gaussian diffusion tensor,

318   whereas γ⊥ was derived by an average of the other two orthogonal projections (De Santis et al.,

319   2011).

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321

2.5   Post-processing

2.5.1   Image registration

324   A registration pipeline similar to that proposed by *Timmers et. al* (Timmers et al., 2016) was used. Briefly, a

325   population-specific   template   was   obtained   with   DTI-TK   software   (available   on

326   http://www.nitrc.org/projects/dtitk). The algorithm applies a deformable registration to the DTI-derived

327   eigenvalues and improves the registration outcome compared to analogous algorithms based on FA maps

328   (Zhang et al., 2006; Keihaninejad et al., 2013, Wang et al., 2011). The resulting normalized images were

329   used to compute the standard *FA*, *MD*, $D_{//}$ and $D_\perp$ maps with a higher resolution compared to the original

330   maps (voxel size $=1 \times 1 \times 1$ mm^3).

331   The TBSS tool of FSL (Smith et al., 2006) was used to obtain a mean FA skeleton for the WM

332   tracts common to all subjects in the normalized space. The threshold limit value of this skeleton was

333   set to 0.4 in order reduce bias due to cross subject variability of the WM tracts. Finally, the

334   participant-specific transformation fields, obtained during the tensor-based transformation, were

335   used to normalize all the other diffusion metrics used in this study as specified by Timmers et al. in

336   supplementary methods (Timmers et al., 2016).

337

2.5.2   ROI based analysis

339   Analysis of the correlation between diffusion metrics and subjects' age was performed on a region

340   of interest (ROI) basis using a hierarchical approach in order to better understand the spatial patterns

341   of aging (Simmonds et al., 2014, Chang et al., 2015). The age-related modifications were calculated

342   separately for WM ROIs and sub-cortical GM (scGM) ROIs.

343   As regards WM, the global trajectories were first obtained averaging the different metrics along

344   all the voxels belonging to the WM skeleton. Subsequently, two groups of WM regions were

345   selected. Following the nomenclature proposed by Simmonds *et al.*, the "core tracts" were selected

346   as the intersection of the WM skeleton and the JHU-DTI81 atlas (Mori et al., 2008). The "cortical

12

347 regional termination zones" (RTZs) were defined as the intersection of the cortical GM regions
348 derived from the Harvard-Oxford (HO) atlas in FSL and the WM skeleton. The two groups of WM
349 tracts were further partitioned in sub-tracts. The core tracts were divided using the JHU's own
350 parcellation (http://www.loni.usc.edu/ICBM/Downloads/Downloads_DTI-81.shtml). The cortical
351 RTZs were divided into frontal, sensory-motor, parietal and occipital tracts. All the above steps are
352 summarized in Figure 2.

353 Regarding the scGM ROI analysis, the HO subcortical atlas was used to identify the different
354 structures. To avoid partial volume effects each element from the atlas was eroded via the "-ero"
355 routine of fslmaths in FSL, using a spherical filter with a 2 mm radius. Because of the limited field
356 of view in the axial direction, only the inner structures of the subcortical GM were retained for the
357 analysis. The caudate, the thalamus, the putamen and the pallidum were considered in the study. In
358 addition, a global trajectory was obtained from the average of all voxels belonging to the examined
359 regions.

360 The average of each diffusion metrics was then calculated for each ROI. The association between
361 the resulting values and the subjects' age was assessed *via* linear regression using the free software
362 R (R Core Team 2013 http://www.R-project.org/). Also, the shared variance between any two
363 metrics was assessed for the global trajectories. Correlation was considered statistically significant
364 when the derived p-value was ≤ 0.05 after correcting for family-wise error ($p_{fwe} \leq 0.05$), *i.e.*
365 multiplying p by the number of regions considered in the group under analysis.
366   p-value ≤ 0.05 without controlling for family-wise error ($p \leq 0.05$) were also reported for
367 comparison with relevant regions highlighted in previous studies (Billet et al. 2015, Kodiweera et
368 al. 2016).
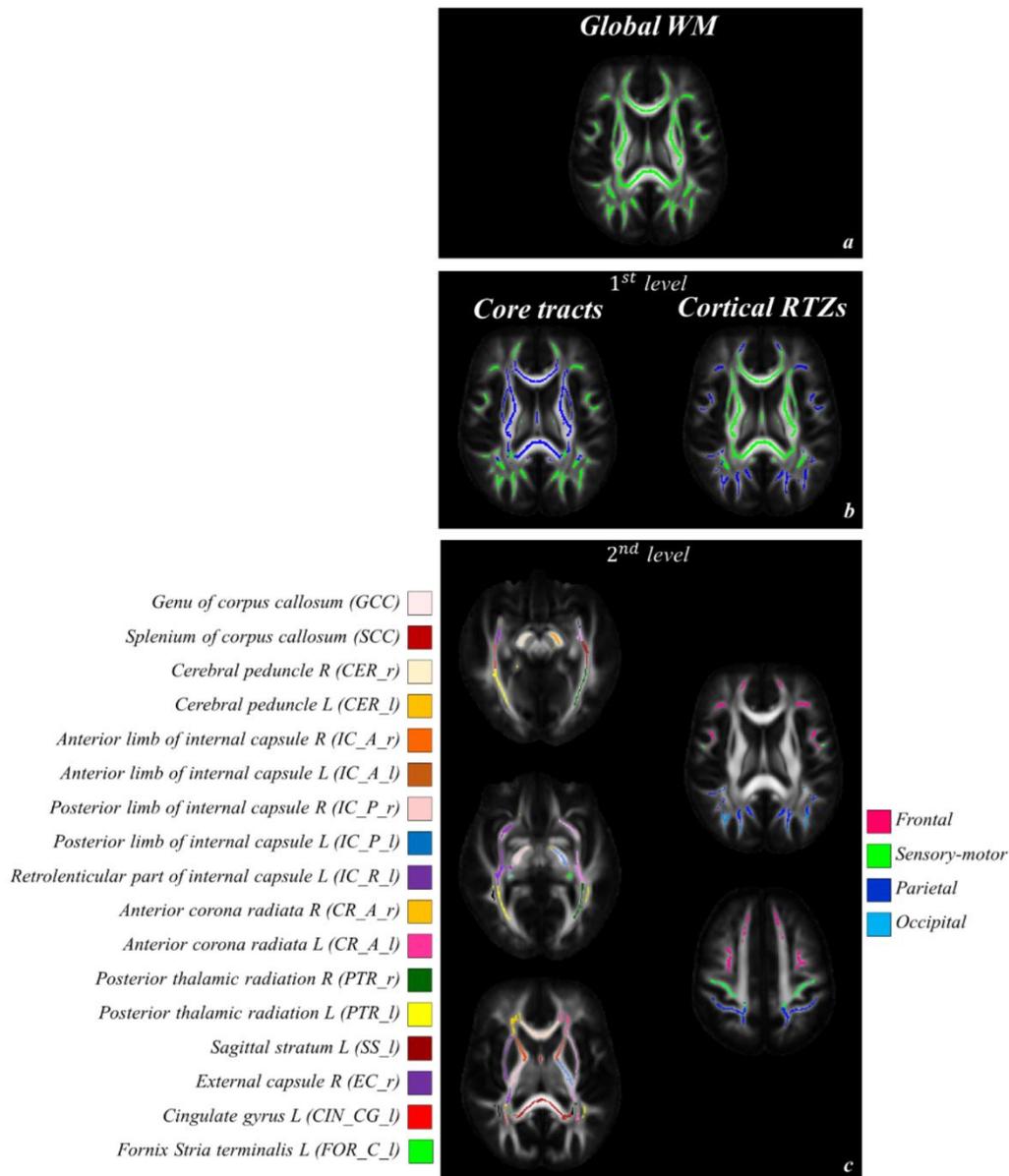
Figure 2: WM atlas description to illustrate the multi-level ROI-based approach used to analyze and display the results. *a*) the global WM atlas is defined by the skeleton obtained with the skeletonize command of FSL using a threshold of 0.4. *b*) In the first level of the subdivision the core tracts are obtained from the intersection between the WM skeleton, the JHU atlas, while the cortical regional termination zones (RTZs) are obtained from the intersection between the WM skeleton and the Harvard-Oxford cortical atlas. *c*) In the second level of the subdivision, the core tracts and cortical RTZs are further divided into sub-regions according to the atlas nomenclatures; 29 sub-regions for the core tracts and 4 for the cortical RTZs were identified. Only those regions are reported that share at least one association between diffusion metrics and aging.

2.5.3   Voxel-wise analysis

To test the effect of aging on the diffusion metrics voxel-wise, permutation-based statistics was carried out on both the WM and scGM. All diffusion metric maps were performed with the WM
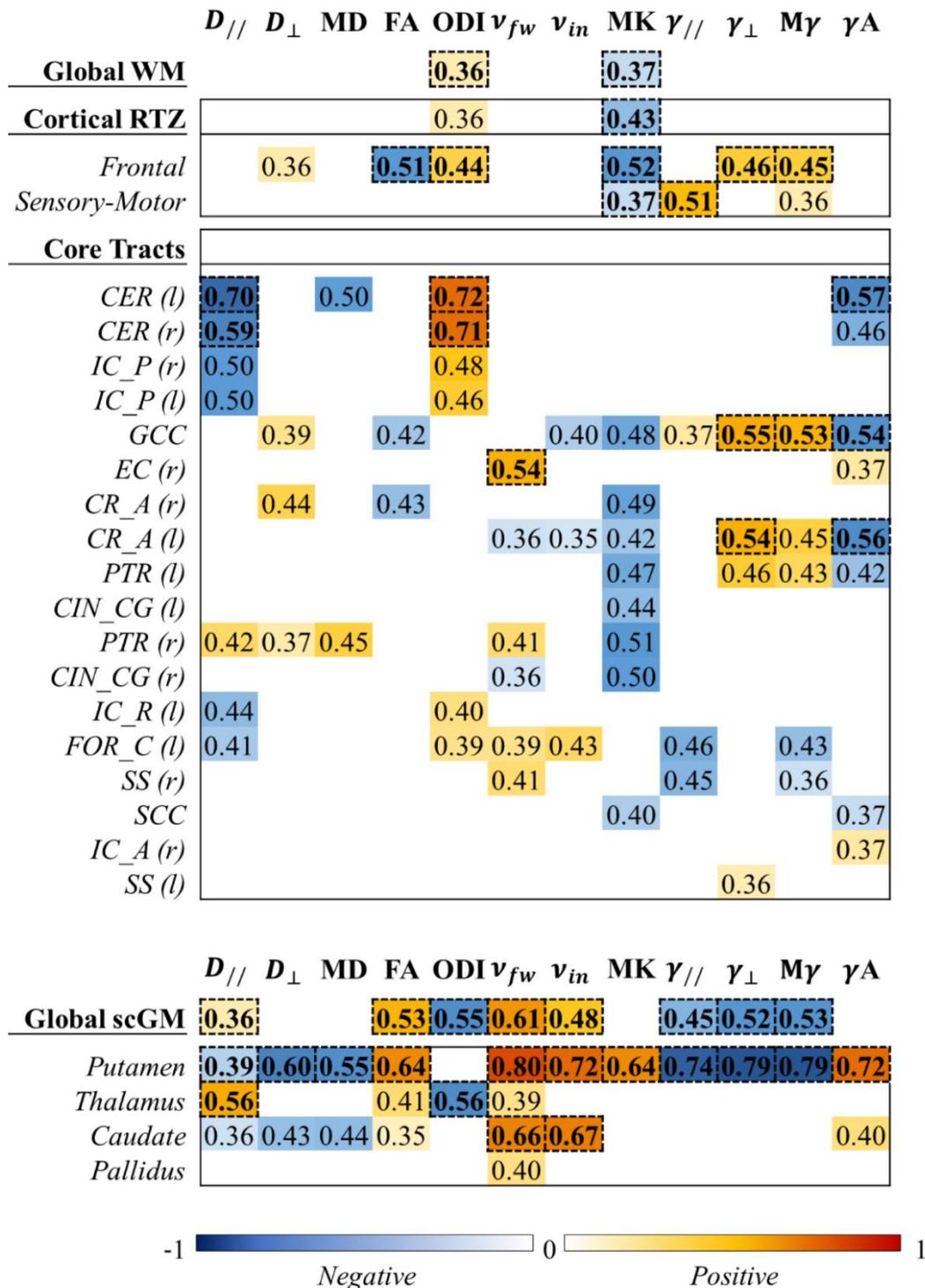
384 skeleton and the scGM eroded mask, respectively. FSL's randomize command was used with 5000

385 permutations to generate the statistic maps. The Threshold-Free Cluster Enhancement (TFCE)

386 option was used to correct p-values for family wise errors ($p_{fwe} \leq 0.05$).

387

3   Results

3.1   ROI analysis

390 To display the results, we used a figure format like the one used by Billet et al. (Billiet et al., 2015).

391 For each ROI and each diffusion metrics we reported the correlation coefficient when $p < 0.05$.

392 Red-yellow colors stand for positive correlation, while blue-cyan colors stand for negative

393 correlation. The regions, where a linear correlation with a family-wise error corrected p-value was

394 found significant ($p_{fwe} < 0.05$), are highlighted in bold and by boxes with dashed contours. Figure 3

395 shows the results for WM ROIs (at the top) and scGM (at the bottom), whereas Figure 4 shows plots

396 of different diffusion metrics *vs* subjects' age in different regions of WM and scGM.

	$D_{//}$	$D_\perp$	MD	FA	ODI	ν_{fw}	ν_{in}	MK	$\gamma_{//}$	$\gamma_\perp$	Mγ	γA
Global WM					0.36			0.37				
Cortical RTZ					0.36			0.43				
Frontal		0.36		0.51	0.44			0.52		0.46	0.45	
Sensory-Motor								0.37	0.51		0.36	
Core Tracts												
CER (l)	0.70	0.50			0.72							0.57
CER (r)	0.59				0.71							0.46
IC_P (r)	0.50				0.48							
IC_P (l)	0.50				0.46							
GCC		0.39		0.42		0.40	0.48	0.37	0.55	0.53		0.54
EC (r)						0.54						0.37
CR_A (r)		0.44		0.43				0.49				
CR_A (l)						0.36	0.35	0.42	0.54	0.45		0.56
PTR (l)								0.47	0.46	0.43		0.42
CIN_CG (l)								0.44				
PTR (r)	0.42	0.37	0.45			0.41		0.51				
CIN_CG (r)						0.36		0.50				
IC_R (l)	0.44					0.40						
FOR_C (l)	0.41				0.39	0.39	0.43	0.46		0.43		
SS (r)						0.41		0.45		0.36		
SCC								0.40				0.37
IC_A (r)												0.37
SS (l)									0.36			

	$D_{//}$	$D_\perp$	MD	FA	ODI	ν_{fw}	ν_{in}	MK	$\gamma_{//}$	$\gamma_\perp$	Mγ	γA
Global scGM	0.36			0.53	0.55	0.61	0.48		0.45	0.52	0.53	
Putamen	0.39	0.60	0.55	0.64		0.80	0.72	0.64	0.74	0.79	0.79	0.72
Thalamus	0.56			0.41	0.56	0.39						
Caudate	0.36	0.43	0.44	0.35		0.66	0.67				0.40	
Pallidus						0.40						

Figure 3: ROI-based results obtained using the multi-level ROI-based analysis in white matter (WM), at the top, and subcortical gray matter (scGM), at the bottom. The colored cells indicate the regions where a correlation between a diffusion parameter and age was found ($p < 0.05$). Warm colors indicate positive correlation, while cold colors indicate negative correlation. Regions showing a significant correlation after correction for family-wise errors are highlighted in bold and by boxes with dashed contours.

3.1.1   Results in WM

$D_{//}$ and *FA* are the only parameters of DTI metrics that show significant correlation with aging, exhibiting mostly a negative association. $D_{//}$ tends to decrease with aging in the cerebral peduncle (CER), while FA presents a decrease in frontal WM. Regarding the parameters obtained using higher b-shells, *MK* shows a negative association, while ODI and v_{fw} of NODDI positively correlate with aging. v_{in} shows weak negative trends within the genu of corpus callosum (GCC) and the left anterior corona radiata (CR_A (*l*)) but a positive trend in the left fornix stria terminalis (FOR_C   (*l*)).
All γ metrics show at least one significant correlation. $\gamma_{//}$, $\gamma_{\perp}$ and *Mγ* generally increase although $\gamma_{//}$ and *Mγ* show a decrease in the left retrolenticular part of the internal capsule (IC_R (*l*)) and right sagittal striatum (SS (*r*)). On the other hand, *γA* generally decreases with advancing age (see Figures 3 and 4).
As regard the global WM atlas, ODI and MK were the only parameters showing a significant trend. The MK decrease seemed to be driven by a decrease within the cortical RTZs rather than in the core tracts. In particular, the tracts close to the frontal lobe showed the greatest number of significant differences. FA and MK decreased while ODI, $\gamma_{\perp}$ and *Mγ* increased. MK decreased also in the tracts close to the sensory-motor lobe along with a parallel increase in $\gamma_{//}$. No general trends related to core tracts were observed, however several region-specific trends were recognized within the parcellation. On average, the regions showing the strongest correlation were the left and right sides of the CER. Here, a simultaneous decrease in $D_{//}$ and increase in ODI were observed. Also, a significantly decreased anisotropy in γ was observed. The same pattern of decreased axial diffusivity and increased ODI applied also to both sides of the internal capsule (IC_P), although not statistically significant. γ-derived parameters showed a rather strong correlation within the GCC and (CR_A (*l*)). Among these metrics, $\gamma_{\perp}$ seemed to be the driving one inducing an increase in *Mγ* and a decrease in *γA*. A positive association was found in the left external capsule between v_{fw} and age. As regards MK, several negative trends were observed within the core tracts, but none of them were strong enough to be considered significant.
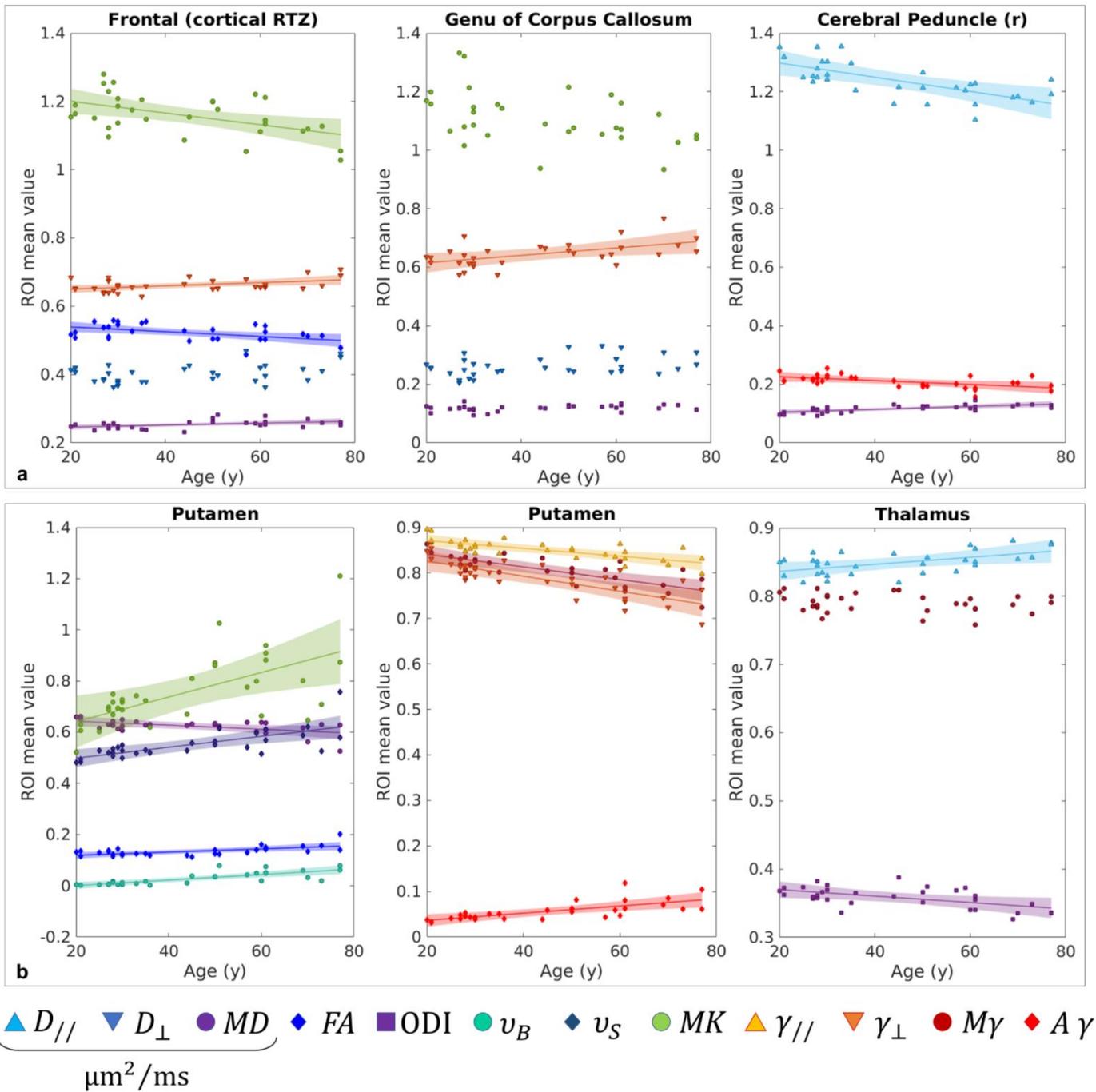
Figure 4: Plots of different diffusion metrics *vs* age in different regions of WM and scGM. Box *a* shows the trends in WM: the frontal part of the cortical RTZs, the left cerebral peduncle (CER (*l*)) and the genu of corpus callosum (GCC) are reported. Box *b* shows the trends in scGM. The trends within the putamen and the thalamus are reported. On the top-right panel the markers and colors identifying the different parameters. Solid lines are reported where a statistical significance was found ($p_{fwe} < 0.05$.) The shaded area represents the confidence interval of 95%.

3.1.2 Results in subcortical GM

Besides a few cases, a complete inversion of age-related trends was observed for all the parameters in the sub-cortical regions (Figure 3): $D_\perp$, MD, ODI, $\gamma_{//}$, $\gamma_\perp$ and $M\gamma$ showed a decrease, whereas FA,

18

445　v_{in}, v_{fw}, γA showed an increase with age. $D_{//}$ showed a positive and negative association with age in

446　the thalamus and in the putamen, respectively. The putamen was with no doubt the region showing

447　the most widespread and strongest correlation with diffusion derived parameters (*i.e.* all apart from

448　ODI). The thalamus showed a pattern similar to that of the CER, but inverted, *i.e.* increased $D_{//}$ and

449　decreased ODI. Finally, the caudate showed a parallel increase in v_{in} and v_{fw} with aging.

450　**3.2　Voxel-wise analysis**

451　The results of the voxel-wise approach were coherent with those found using the ROI-based

452　approach. Regional differences in WM are displayed in Figure 5. $D_{//}$ and ODI showed mono-lateral

453　differences in the left cerebral peduncle and in the left posterior limb of the internal capsule. This

454　result may highlight a possible associated variation of $D_{//}$ and ODI (Billiet et al. 2015). A general

455　increase in $M\gamma$ and $\gamma_\perp$ *vs* age was also highlighted (Figure 5). The effects are widespread in the left

456　frontal area, including the left corona radiata and part of the genu of corpus callosum. In accordance

457　with the results found in the ROI-based analysis, v_{in} showed a significant increase within the right

458　external capsule. No significant association between MK and age was found in the WM voxel-wise

459　analysis.

460　Figure 6 shows the trends of the conventional DTI-parameters and NODDI-parameters in scGM. In

461　the putamen, a decrease in MD together with an increase in FA, v_{in} and v_{fw} were observed. v_{in}

462　increased also in the caudate, while an increase in v_{fw} was observed in the posterior part of the

463　thalamus. ODI decreased in the thalamus with a spotty pattern. The voxel-wise correlations of γ-

464　derived metrics *vs* age in scGM are highlighted in Figure 7. The strong increase in $M\gamma$ and decrease

465　in γA seemed to be driven by a variation in $\gamma_\perp$, rather than $\gamma_{//}$.

466

467　**3.3　Correlation between metrics**

468　The squared values of linear cross-correlation coefficients calculated between metrics both in total

469　WM and total scGM are displayed in Figure 8. These values represent the amount of variance that

470　each metrics shares with the others, giving an estimate of how unique the information provided by

471　each metrics is. As expected, the variance shared by parameters derived from the same metrics is

472　high. In WM, $D_\perp$ seems to account for most of the variability of FA and MD. v_{in} shares a large

473　portion of variance with all the DTI parameters and specifically with MD and $D_\perp$, while ODI has a

474　negative association with D//. MK shares a rather high portion of variance with MD, FA, and $D_\perp$. γ-

475　derived parameters have a rather small portion of variance shared with the other diffusion metrics.

476　The only exception is $\gamma_{//}$ that shows a stronger association with MD, FA and MK.

477　The right side of Figure 8 shows the results for scGM. The results appear to be clustered in a

478　different way. MD and FA on the one hand and $M\gamma$ and γA on the other, share a large proportion of

variance with $D_\perp$ and $\gamma_\perp$, respectively. ODI measure shows a negative correlation only with D// and

480 FA. All the metrics obtained using higher b-shell seem to share a larger portion of variance. In

481 particular, ν_{in} and ν_{fw} show a much higher association with γ-metrics, compared to that shown in

482 WM.

483
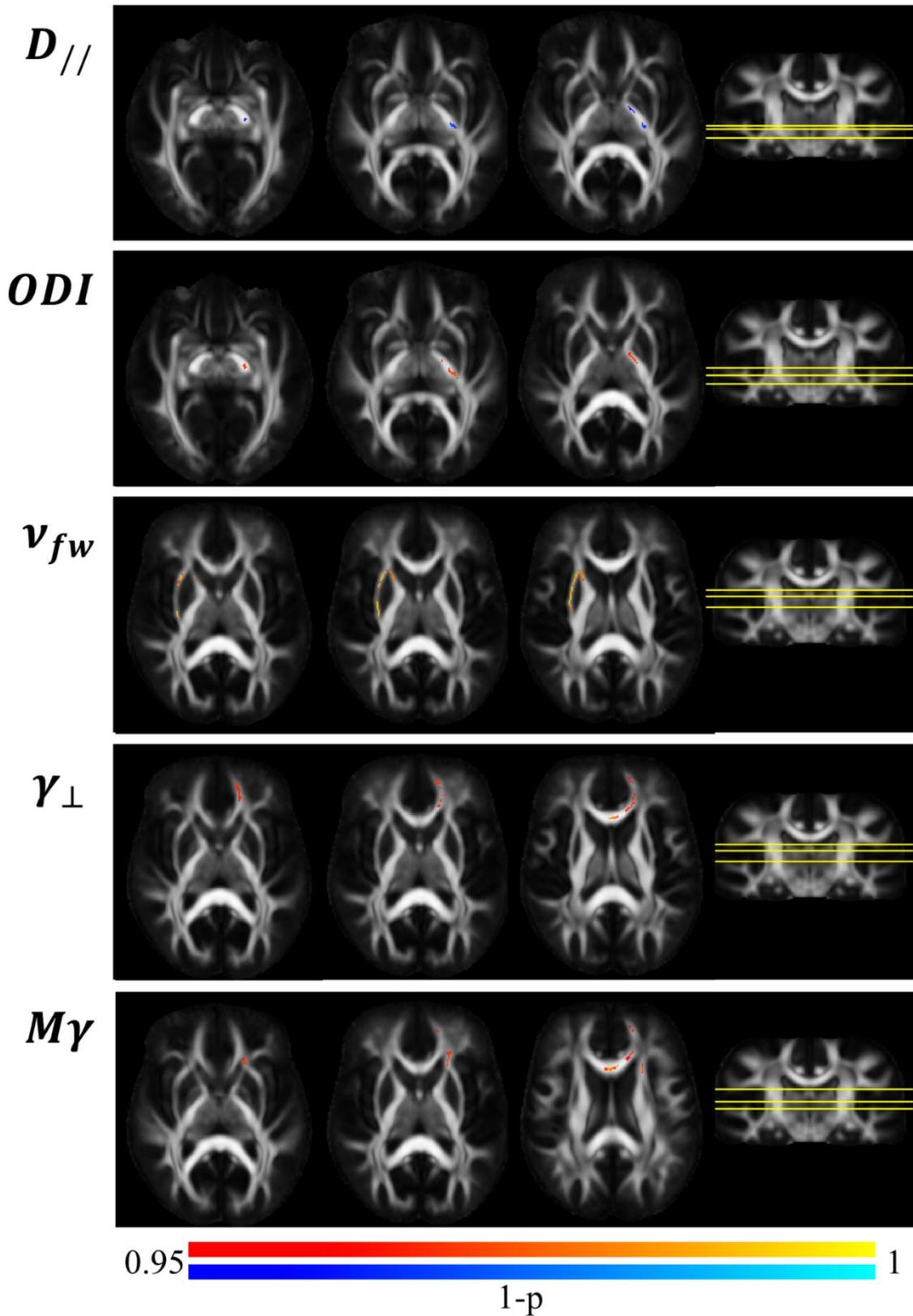
Figure 5: Results of the voxel-wise analysis of DTI-, NODDI- and γ-metrics correlation with
subjects' age in WM. The maps show the corrected p-value $(1-p)$ superimposed on the population
specific *FA* template. The red-yellow colors denote positive correlation, while the blue-cyan colors
denote negative correlation.
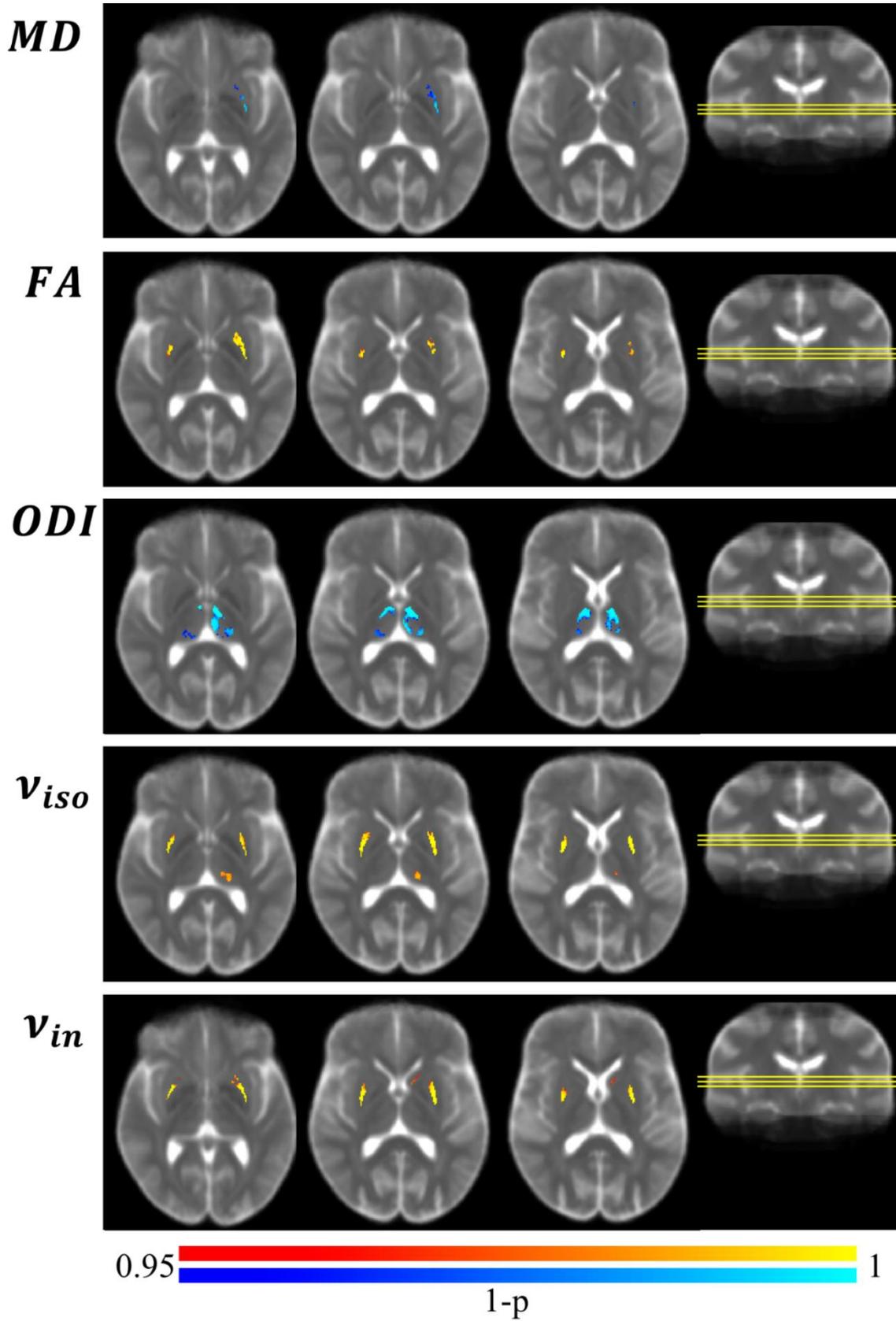
489 **Figure 6:** Results of the voxel-wise analysis of correlation between DTI- and NODDI-derived
490 parameters and subjects' age in scGM. Here the results are superimposed on *MD* population specific
491 template. The red-yellow colors denote a positive correlation, while the blue-cyan colors denote a
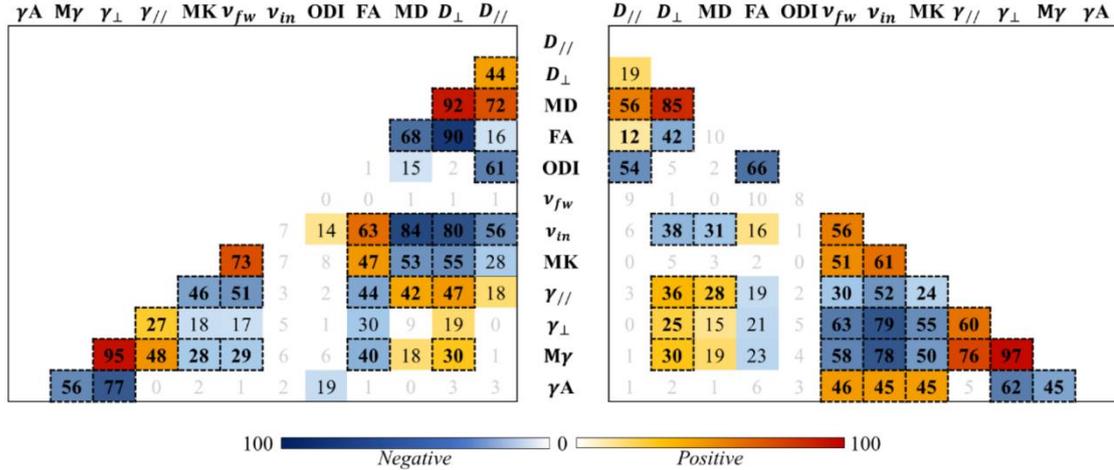492 negative correlation.
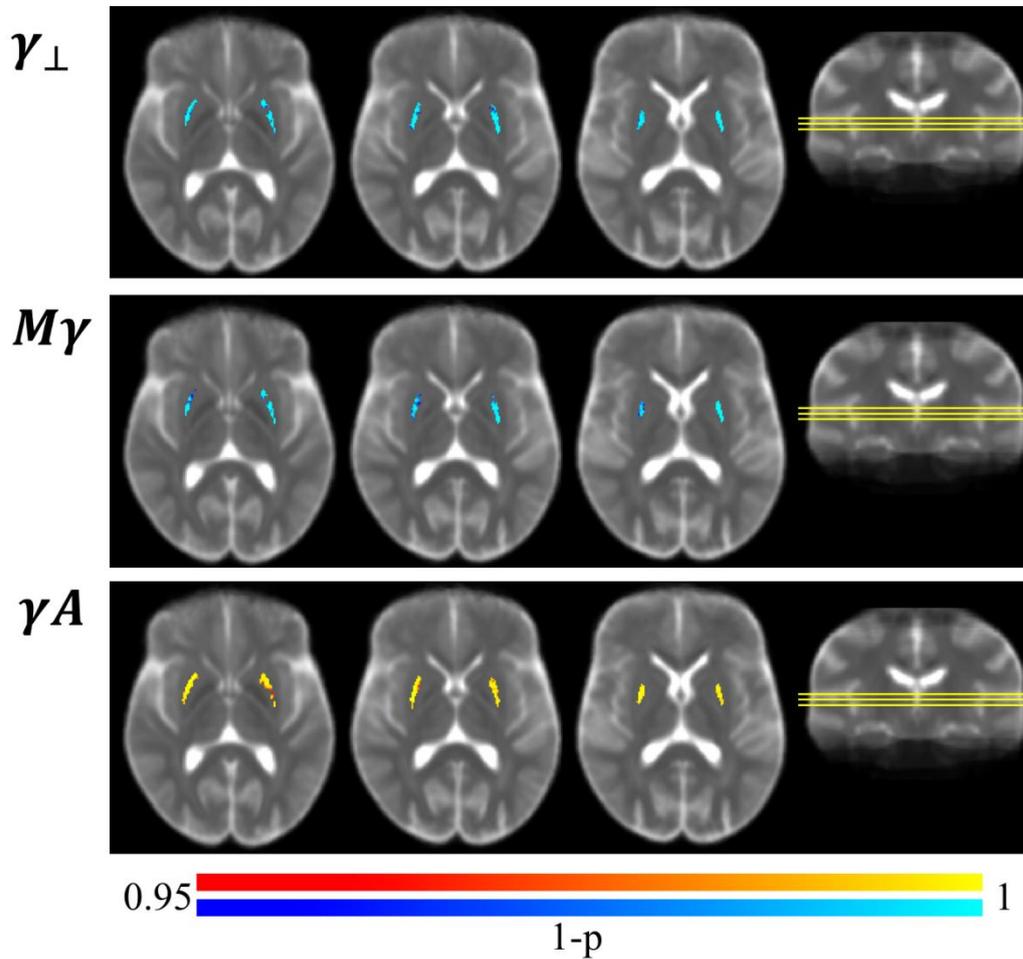
493

494 **Figure 7:** Results of the voxel-wise analysis of correlation between γ-metrics and subjects' age in
495 scGM. The results are superimposed on *MD* population template. The red-yellow colors denote a
496 positive correlation, while the blue-cyan colors denote a negative correlation.

497

498

499

Figure 8 — Shared variance between diffusion metrics

Global WM

	γA	Mγ	γ⊥	γ//	MK	ν_fw	ν_in	ODI	FA	MD	D⊥	D//
$D_{//}$												
$D_{\perp}$												44
MD										92	72	
FA									68	90	16	
ODI								1	15	2	61	
ν_{fw}							0	0	1	1	1	
ν_{in}						7	14	63	84	80	56	
MK						73	7	8	47	53	55	28
$\gamma_{//}$					46	51	3	2	44	42	47	18
$\gamma_{\perp}$				27	18	17	5	1	30	9	19	0
Mγ			95	48	28	29	6	6	40	18	30	1
γA		56	77	0	2	1	2	19	1	0	3	3

Global scGM

	D//	D⊥	MD	FA	ODI	ν_fw	ν_in	MK	γ//	γ⊥	Mγ	γA
$D_{//}$												
$D_{\perp}$	19											
MD	56	85										
FA	12	42	10									
ODI	54	5	2	66								
ν_{fw}	9	1	0	10	8							
ν_{in}	6	38	31	16	1	56						
MK	0	5	3	2	0	51	61					
$\gamma_{//}$	3	36	28	19	2	30	52	24				
$\gamma_{\perp}$	1	25	15	21	5	63	79	55	60			
Mγ	1	30	19	23	4	58	78	50	76	97		
γA	1	2	1	6	3	46	45	45	5	62	45	

100 — Negative — 0 — Positive — 100

Figure 8: The shared variance between diffusion metrics is displayed separately for white matter (WM), on the left, and subcortical gray matter (scGM), on the right. The higher the reported value, the higher the similarity of the information provided by the two metrics. Warm colors show positive correlation, cold colors represent negative correlation. Significant correlation, corrected for family-wise errors, are highlighted in bold and by a box with dashed contours.

4   Discussion

In this cross-sectional study we assessed the potential of a combined use of γ-metrics and other more widespread diffusion MRI (dMRI) techniques in detecting the microstructural and physiological changes due to normal aging in WM and scGM of the human brain. Previous works (Caporale et al. 2017) highlighted how γ-metrics may reflect inhomogeneities due to $\Delta\chi$ among various tissues and compartments, being potentially useful as an indirect measure of myelin integrity and iron content. In this paper, the cohort of volunteers spanned from young adults to elderly subjects. To analyze the different regions of the brain, we used a hierarchical ROI-based approach in parallel with a voxel-wise-based approach, both in WM and scGM. We found diversified patterns of parameter modifications with advancing age, both in scGM and WM, possibly indicating regional-specific aging processes. The results suggest that γ-metrics is complementary to DTI, DKI and NODDI, highlighting changes not significantly detected by the other conventional metrics.

4.1   Microstructural changes in white matter

The results of this study suggest that a combination of different dMRI-derived techniques permits observation of microscopically different aging patterns within the WM fibers.

 The aging of WM fibers appears to be driven by two principal mechanisms: the degradation of nerve fibers and the degeneracy of the myelin (Peters, 2009, Peters and Kemper, 2012). On one

hand, degenerating nerve fibers start to accumulate mixtures of organelles and neurofilaments. These accumulations are often related to dystrophy of the axons such as swelling. The degeneration process ends with the complete disintegration of the axon. The extent of lost fibers, in some specific regions of rhesus monkeys' brains, has been quantified to be around 20% in the genu of corpus callosum, 30% in the splenium of corpus callosum and 45% in the anterior commissure (Sandell and Peters, 2003, Bowley et al., 2010). On the other hand, myelin undergoes segmental demyelination that is often followed by remyelination and sometimes by myelin decompaction. Remyelinated segments are thinner and shorter, while decompaction is principally caused by splitting of myelin in the major dense line (Peters, 2009, Peters and Kemper, 2012, Sandell and Peters, 2003, Bowley et al., 2010).

dMRI has been extensively used with the aim to track these microscopic changes in vivo. A large number of cross-sectional studies (Pfefferbaum et al., 2000, Abe et al., 2002, Salat et al., 2005, Sullivan et al., 2010, Ardekani et al., 2007, Giorgio et al., 2010), but also longitudinal studies (Barrick et al., 2010) reported an increase in MD and a decrease in FA. Specifically, FA modifications seem to be mostly related to grater $D_\perp$ rather than $D_{//}$ (Zhang et al., 2010, Bartzokis et al., 2012), suggesting that the FA reductions are linked to myelin degradation and axonal loss. However, some authors pointed out that care should be taken when interpreting these results (Wheeler-Kingshott and Cercignani, 2009).

MK has been shown to decrease with aging (Lätt et al., 2013, Gong et al.,2014, Coutu et al., 2014) indicating a less complex organization of tissues in elderly brains. However, Billet et al. (Billet et al., 2015) reported contrasting results showing an increased MK with ageing. However, the investigated age-range was narrower compared to the population studied by the above-mentioned authors.

Few studies reported the association between NODDI parameters and aging (Billet et al., 2015, Cox et al., 2016). v_{fw} was observed to decrease in both studies, while contradictory results were reported for v_{in} and ODI: Billet et al. reported an increase in both these parameters, while Cox et al. reported a decrease in both cases. However, the two studies dealt with different age ranges. In a study carried out on a cohort of young to middle-aged adults, Kodiweera et al (Kodiweera et al., 2017) reported an increase in ODI with aging and observed how this parameter was the most sensitive to microstructural changes compared to DTI parameters.

In order to explain the overall trends of age-related microscopic changes, several neurodegenerative theories have been proposed in the past years. For example, it has been established that age-related

557   modifications occur with frontal predominance (Abe et al., 2002, Salat et al., 2005, Ardekani et al.,

558   2007, Sullivan et al., 2010), thus an anterior-posterior gradient of degeneration has been proposed

559   (Pfefferbaum and Sullivan, 2006). On the other hand, according to the retrogensis theory,

560   demyelination is the major driving mechanism of degeneration and the late myelinating fibers are

561   more affected than the early myelinating ones (Stricker et al., 2009, Cox et al., 2016). Finally, the

562   Wallerian degeneration theory proposes that axonal degradation is the result of injuries happening

563   further from the degradation site (Damoiseaux et al., 2009, Davis et al., 2009).

564

565

566

567   **4.1.1   Is γ-imaging sensitive to myelin degradation?**

568   In the past years, *in vitro*, *ex vivo* and *in vivo* experiments were performed to investigate the features

569   of the so called pseudo-superdiffusion γ parameter (Palombo et al. 2011; Palombo et al 2012;

570   Capuani et al. 2013; Caporale et al. 2017). The experiments coherently showed that γ quantifies

571   water molecules diffusing with a wide distribution of diffusion lengths in heterogeneous and multi-

572   scale tissues. The width of this set of diffusion lengths is partially due to water diffusion

573   compartmentalization, but also to the inhomogeneity (or averaged internal gradients g_{int}) coming

574   from local $\Delta\chi$ between compartments. In the human brain, $\Delta\chi$ arises from differences in non-heme

575   iron contents and iron-storage proteins and from various degrees of myelin density and orientation

576   with respect to B_0. It has been found that γ values decreased in parallel to $\Delta\chi$-derived g_{int} increase

577   (Palombo et al. 2011; Palombo et al 2012; Capuani et al. 2013; Caporale et al. 2017). Moreover, by

578   repeating the γ-imaging studies in the brain of distinct groups of healthy subjects, using acquisitions

579   obtained with a different number of diffusion gradient directions, we found an excellent agreement

580   between the mean γ values representative of certain brain regions (De Santis et al. 2011;

581   GadElkarim et al. 2013; Caporale et al. 2017).

582   Our results show a significant increase in $\gamma_\perp$ as a function of age in frontal WM and more

583   specifically in the genu of corpus callosum and anterior corona radiata (figures 3, 5). We suggest

584   that these results which are in agreement with our previous findings (Caporale et al. 2017), may

585   reflect an effective decrease in the thickness and integrity of the myelin sheaths across the densely

586   packed WM fibers. Indeed a reduction of myelin would affect the g_{int} between the myelinated axons

587   to which γ parameters are sensitive, in at least two ways: first, decreasing the value of the magnetic

588   susceptibility of axons compared to that of the surrounding tissues and thus inducing a decreased

589   $\Delta\chi$; second, inducing a more prominent averaging effect of the diffusion on the inhomogeneities

590   induced by Δχ by increasing the space between the axons (Mitchell et al. 2010; Di Pietro et al.

591   2014). The overall effect would thus be a decrease in the magnitude of internal gradients g_{int} with a

592   consequent increase in γ.

593   Our speculations may be supported by other studies using different MRI techniques. For example,

594   the decrease in magnetization transfer (MT) is associated with loss of macromolecular content,

595   typically myelin. Two different studies (Dragansky et al., 2011, Callaghan et al., 2014) using a

596   quantitative MT approach to study brain aging, showed regional patterns of decreased MT similar to

597   those observed in our voxel-wise analysis of $M\gamma$ and $\gamma_\perp$.

598   Neither kurtosis nor DTI, and NODDI metrics showed significant correlations with age within the

599   genu and the anterior corona radiata, suggesting the complementarity of the γ metrics compared to

600   the other dMRI metrics in these regions.

601

602   **4.1.2   ODI increase and $D_{//}$ associated to axonal loss**

603   The present study also found a significant age-related decrease in $D_{//}$ as well as an increase in ODI

604   within the cerebral peduncle (CER), bilaterally, on a ROI-based analysis. The same significant

605   trends were found in the voxel-based analysis within the left CER and left IC_P. Other studies using

606   a TBSS approach on DTI-derived maps reported similar correlations of $D_{//}$ in the IC_P (Kawaguchi

607   et al., 2010) and both in the CER and the IC_P (Burzynska et al., 2010). In a study using both

608   NODDI and standard DTI metrics, Billet et al. (Billiet et al., 2015) reported a similar pattern of

609   decreased $D_{//}$ and an increased ODI with aging in these regions. However, this decrease was not

610   statistically significant.

611   This pattern of changes could reflect microscopic aging processes different from those described in

612   the previous section. However, in order to form a hypothesis about the microscopic modifications

613   causing these parameter changes, it is useful to understand the anatomical composition of the IC_P

614   and the CER. These regions are mainly formed by three fiber tracts: the corticospinal, the

615   corticobulbar and the corticopontine. These tracts are components of the projection fibers

616   interconnecting cortical areas with deep nuclei, brain stem, cerebellum and spinal cord. They

617   originate in the cerebral cortex and converge through the corona radiata to form the IC_P in a

618   tightly compact bundle, oriented in a superior-inferior direction. Subsequently, the fibers enter the

619   cerebral peduncle and continue their ways toward different destinations (Jellison et al., 2004).

620   Supposing that the projection fibers are markedly affected by aging, a lowered axial diffusivity may

621   be explained by axonal degeneration processes. Indeed, the beginning of the degeneration is

622   characterized by accumulation of organelles, such as lysosomes and mitochondria, as well as an

623   increase in neurofilament density within the axoplasm, thus hindering water molecule diffusion

624 along the axons (Peters, 2009, Peters and Kemper, 2012). Furthermore, the axons undergo

625 dystrophic changes such as swelling and beading, which have been shown to induce a reduction in

626 $D_{//}$ (Budde and Frank, 2010; Palombo et al. 2017). The space left empty by damaged fibers would

627 thus be occupied by crossing fibers less affected by aging, such as the fibers of the pontocerebellar

628 tract in the cerebral peduncle (Kamali et al., 2010) and those of the corticothalamic tract in the IC_P

629 (Axer and v Keyserlingk, 2000), thus contributing to a decrease in axial diffusivity and explaining

630 the parallel increase in orientation dispersion.

631 4.1.3 WM modifications in the context of neurodegenerative theories

632 The results obtained in the cortical RTZs as well as those obtained in the genu of corpus callosum

633 and the corona radiata are in line with the hypothesis of posterior-anterior gradient of degeneration.

634 The greatest correlation between parameters and age was found near the frontal lobe of the cortical

635 RTZs. The decrease in FA, and MK in frontal WM as well as the increase in ODI are coherent with

636 previous studies and the complementary increase in $M\gamma$ and $\gamma_{\perp}$ with aging well fit a scenario of

637 decreased microstructural complexity, driven by axonal loss and demyelination.

638 The results obtained in the CER and the IC_P are coherent with the Wallerian hypothesis

639 suggesting that axonal degradation can contribute to the overall degenerating age-related process.

640 Neither our results nor the interpretations that we are proposing are in open contradiction with the

641 retrogenesis hypothesis. The genu is known to myelinate later than other fibers, while the CER and

642 the IC_P that are early myelinating fibers (Kinney et al., 1988, Label et al., 2008), undergo a

643 degeneration process different from demyelination.

644

645 4.2 Microstructural variations in subcortical gray matter

646

647 In scGM structures we observed a not uniform pattern of parametric correlation with aging,

648 possibly revealing regional-specific microscopic modifications.

649 4.2.1 The putamen

650 From a microscopic point of view, the putamen has a relatively simple structure. It is composed by

651 neurons with a thickly spherical arborization, which is densely covered with dendritic spines

652 (Yelnik, 2002). Nonetheless, in this region we found the strongest association between parameters

653 and age. All parameters correlated with age, apart from ODI: MD, axial and radial diffusivity as

654 well as $M\gamma$, axial and radial γ decreased, whereas all the other metrics increased. These results are

in general agreement with those reported in literature. The increase in FA associated with a decrease in MD has been reported (Bhagat and Beaulieu, 2004, Abe et al., 2008, Pfefferbaum et al., 2010, Xu et al., 2015). Specifically, the increase in FA has been associated with a higher decrease in $D_\perp$, compared with a more preserved value of $D_\parallel$ (Wang et al., 2010). However, the microscopic changes that drive these parameter modifications are still unclear. Some authors observed how they could be related to the volume reduction of the striatum, with concurrent gliosis and tissue compaction (Wang et al., 2010). Other authors argued that iron deposition may significantly affect the measurement of water diffusion in the brain (Pfefferbaum et al., 2010, Xu et al., 2015). Indeed, it is well established that a progressive iron deposition selectively affects scGM (Hallgren and Sourander, 1958; Schipper, 2004, Acosta-Cabronero et al., 2016) and that the putamen presents the strongest age-related increase (Acosta-Cabronero et al., 2016).

Our recent study of healthy young human brain (Caporale et al., 2017) suggested that γ-metrics is sensitive to non-heme iron concentration, especially in sub-cortical GM. The results obtained in scGM reported in the present study, are in good agreement with these previous findings. Indeed, the marked negative trend of $M\gamma$, $\gamma_\parallel$ and $\gamma_\perp$ as a function of age in the putamen may reflect an increasing effect of susceptibility inhomogeneities due to age-related iron accumulation.

According to the literature, an age-related increase in MK within the putamen has been found (Gong et al. 2014). Dependence of the DKI derived metrics on the magnetic field inhomogeneities has already been pointed out (Palombo et al. 2015), so it is likely that the correlation found between the metrics derived by fitting data from the higher b-shells and aging are influenced by the iron deposition. This is corroborated also by the observation that the shared variance between metrics changes when considering WM and scGM. Specifically, in the latter case there is an increase in the variance shared by metrics obtained from the higher b-shells, whereas there is a loss of shared variance between DTI metrics and the others. γ metrics showed a higher correlation with age compared to MK, this is likely due to the higher b-values used. These metrics are likely to be more sensitive to iron deposition. It remains to be understood to what extent these changes are influenced by microscopic changes and to what extent they are caused by local changes in the internal gradient. More studies are required to clarify this issue.

4.2.2 The thalamus

The thalamus is the center through which patterns of nerve tracts from cerebral cortex and subcortical and cerebellar regions connect. From a cytoarchitectonical point of view, it is divided

687 into numerous nuclei, each of which reflects a different functional connection with the cortex.
688 Several studies have reported a generalized age-related volume decrease (Raz et al., 2005,
689 Cherubini et al., 2009, Hughes et al., 2012), and it has been observed that some of the subregions
690 undergo differential shape changes with aging, including the anterior, the ventroanterior and the
691 dorsomedial nuclei (Hughes et al., 2012). DTI studies have reported an increase in MD along with a
692 non-significant decrease in FA using both a ROI-based (Cherubini et al., 2009, Hughes et al., 2012,
693 Gong et al., 2014) and a voxel-based approach (Draganski et al., 2011). Also, Gong *et al.* observed
694 a decrease in MK (Gong et al., 2014), but there is no study assessing the association between
695 NODDI parameters and age within the thalamus in the literature. Our results did not highlight MK
696 correlation with age, while they showed a decreased orientation dispersion using both the ROI-
697 based and the voxelwise-based approach as well as an increased axial diffusivity only in the ROI-
698 based approach. The voxelwise results showed a bilateral pattern of ODI increase that is more
699 accentuated in the left thalamus. The most affected regions seem to be the ventro-lateral and ventro-
700 anterior nuclei belonging to the so-called lateral group as well as some nuclei of the medial group
701 such as the center median and parafascicular groups, as defined by Morel *et al*. Microscopically
702 these regions are characterized by a higher concentration of myelinated fibers (Morel et al., 1997,
703 Danos et al., 2003). It has been established that, with aging, the dendritic tree undergoes a
704 progressive regression in GM, implying the reduction in number and length of the branches and the
705 decrease in the number of spines (Scheibel et al., 1975, Nakamura et al., 1985, Dumitriu et al.,
706 2010). In a recent study, comparing histology derived parameters and NODDI derived parameters
707 on spinal cord lesions from patients with multiple sclerosis, it has been shown that ODI well
708 matched its histology counterpart and, furthermore, that a lower ODI in the lesions was indicative of
709 reduced neurite architecture complexity (Grussu et al., 2017). Thus, regression of the dendritic tree
710 combined with relatively unaffected thalamic fibers would cause reduced neurite dispersion as well
711 as increased axial diffusivity, since the extra axonal water would be less hindered along the
712 direction of the fibers. Another possible explanation could be a selective degradation of some fiber
713 bundles.

714 **4.3   Interpretation of the NODDI parameter modifications with aging**
715 We found several associations between NODDI parameters and aging in different brain regions.
716 However, the interpretation of this correlation could be somehow tricky. A recent study showed that
717 some NODDI constraints seemed to be invalid (Lampinen et al., 2017). This inconsistency does not
718 hinder the model from fitting the data, especially in WM and thus the reported associations are
719 thought to be reliable. However, the interpretations of the parameters could be misleading. This

720 should be particularly true for the v_{in} and v_{fw} parameters, while ODI is supposed to be negligibly
721 affected (Zhang et al., 2012, Lampinen et al., 2017).

722

4.4 Methodological considerations

724 Although the studied cohort of subjects covered a broad age range, the total number of volunteers
725 recruited for the present study was smaller compared to other studies focused on aging (Callaghan
726 et al., 2014, Gong et al., 2014, Billet et al. 2015, Cox et a., 2016, Kodiweera et al. 2016). However,
727 our findings related to DTI, NODDI and MK metrics are broadly in accordance with those
728 presented in previous studies of larger cohorts (Billet et al. 2015, Kodiweera et al. 2016, Gong et al.,
729 2014).

730 In this study we assessed association between diffusion metrics and aging using a simple linear
731 regression. Other similar studies suggested that age-related changes follow non-linear trajectories
732 (Billet et al., 2015, Cox et al., 2016). However strong deviations from linear trends have been
733 primarily observed in different age ranges such as in brain maturation (Chang et al., 2015) or
734 including elderly subjects (Cox et al., 2016). Moreover, we found that linear regression well
735 described the trends observed in our data. Further studies involving more and older subjects, (>60y)
736 are needed to investigate higher order differences of γ-metrics with age.

737 Inadequate signal to noise ratio (SNR) can bias diffusion parameter estimation. To validate the
738 reliability of the quantified metrics, we investigated the SNR of our raw DW data as a function of
739 the b-values in WM and scGM (supplementary materials). We found that SNR was above the
740 critical value SNR=3. This should ensure an unbiased quantification of the diffusion metrics
741 obtained using higher b-values (Caporale et., al 2017, Jones et al., 2013).

742 Despite the quantification of γ-metrics requires the acquisition of images with b values higher than
743 those used to obtain DTI, DKI and NODDI metrics, the γ-metrics maps seem to be characterized by
744 a lower contrast to noise ratio than the maps reconstructed with the other metrics. This could affect
745 the accuracy and sensitivity of the technique. However, it should be considered that γ-derived maps
746 are showing different kind of information compared to that of conventional diffusion methods,
747 which apparently varies less across tissues.

748

749 This study suggests the ability of γ-metrics to detect age-related differences due to changes in $\Delta\chi$-
750 driven inhomogeneities. Future studies should corroborate the results of the present study, possibly
751 using other specific quantitative MRI techniques such as quantitative susceptibility mapping (QSM)

752 or magnetization transfer (MT) to compare our technique with the two most common techniques
753 used for quantification of iron deposition and myelin content.

754   The long scanning time required by the diffusion protocol used in this study limits the amount of
755 different acquisitions and it is one of the major issues linked to the achievement of γ-weighted
756 maps. Therefore, the use of performing scanners with parallel acquisition mode is necessary to carry
757 out this type of investigation involving multi-b-value acquisitions. In supplementary materials, the
758 results of a preliminary study investigating the feasibility of using a down sampled protocol (with a
759 halved number of b-values and the same number of directions) are reported. Our preliminary results
760 in supplementary materials show that a protocol with a higher number of b-acquisitions, such as the
761 one used in this study, helps to reduce the variability in the γ extraction and in the bias introduced
762 when using the DTI reference frame approximation to extract the relevant γ-metrics according to De
763 Santis et al. (De Santis et al., 2011). However, the results also showed that by using a reduced
764 number of acquisitions it is still possible to obtain a reliable quantification of γ. Further studies are
765 needed to obtain the best tradeoff between an optimized protocol and reliable maps.

766 In this study we presented several associations between diffusion metrics and age. These
767 correlations don't necessarily imply a causal relationship. It is possible that other factors, such as
768 technical differences between different metrics, alter the sensitivity or accuracy of the fitting to the
769 data. This could potentially mean that the differences in correlations identified in the results are not
770 necessarily related to the ability of the techniques to identify different ageing mechanisms. Further
771 studies are necessary to confirm the conclusions of the present work.

772
773

774 **5   Conclusion**

775 In this study we used DTI, NODDI, MK and γ-metrics to assess physiological (i.e. the iron content)
776 and microstructural (myelin damage, axonal disintegration, neuron cell loss) changes in cerebral
777 WM and scGM of middle- and older-aged subjects. We found that γ-metrics are remarkably
778 sensitive and provide more complementary information than DTI-metrics, MK and NODDI in the
779 detection of frontal changes in the WM. The combined use of these techniques may also reveal
780 different patterns of age-related changes.

781

782 This study suggests that an increase in $\gamma_\perp$ values within WM may reflect myelin degradation, and a
783 decrease in Mγ within scGM, specifically in the putamen, may reflect iron deposit accumulations.
784 Changes in $D_{//}$ and ODI could be indices of axon degradation in the pyramidal tract while reflecting

decreased architecture complexity within the thalamus. This study demonstrates the added value of γ-metrics for assessing microscopic brain alterations due to aging and providing independent measurements that are complementary to the conventional diffusion metrics. In conclusion, γ-metrics combined with other DW-derived metrics can more comprehensively characterize the complex mechanisms underlining age-related changes than conventional diffusion techniques alone.

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Resource data for this article

The data belongs to a larger research project and we are not allowed to share it.

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a
Volunteers: 32 subjects (Age range 20-77y Mean/SD = 44/18y)
Acquisition scheme: 11 b-shells with 15 directions each + b_0

b
Noise correction *(Dwidenoise-MRtrix3)*
Gibbs ringing correction (Kellner *et al.*)
Eddy current correction *(EDDY-FSL)*

c
b up to 1.5 (ms/μm^2)   b up to 2.5 (ms/μm^2)   b up to 5.0 (ms/μm^2)

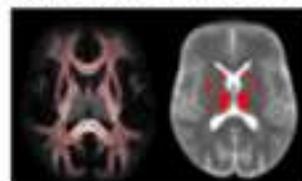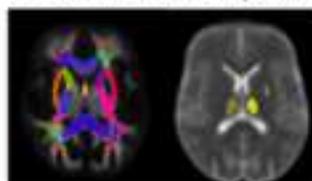DTI   NODDI   DKI γ-imaging

d
Spatial normalization *(DTI-TK)* + mean FA skeleton *(TBSS)*
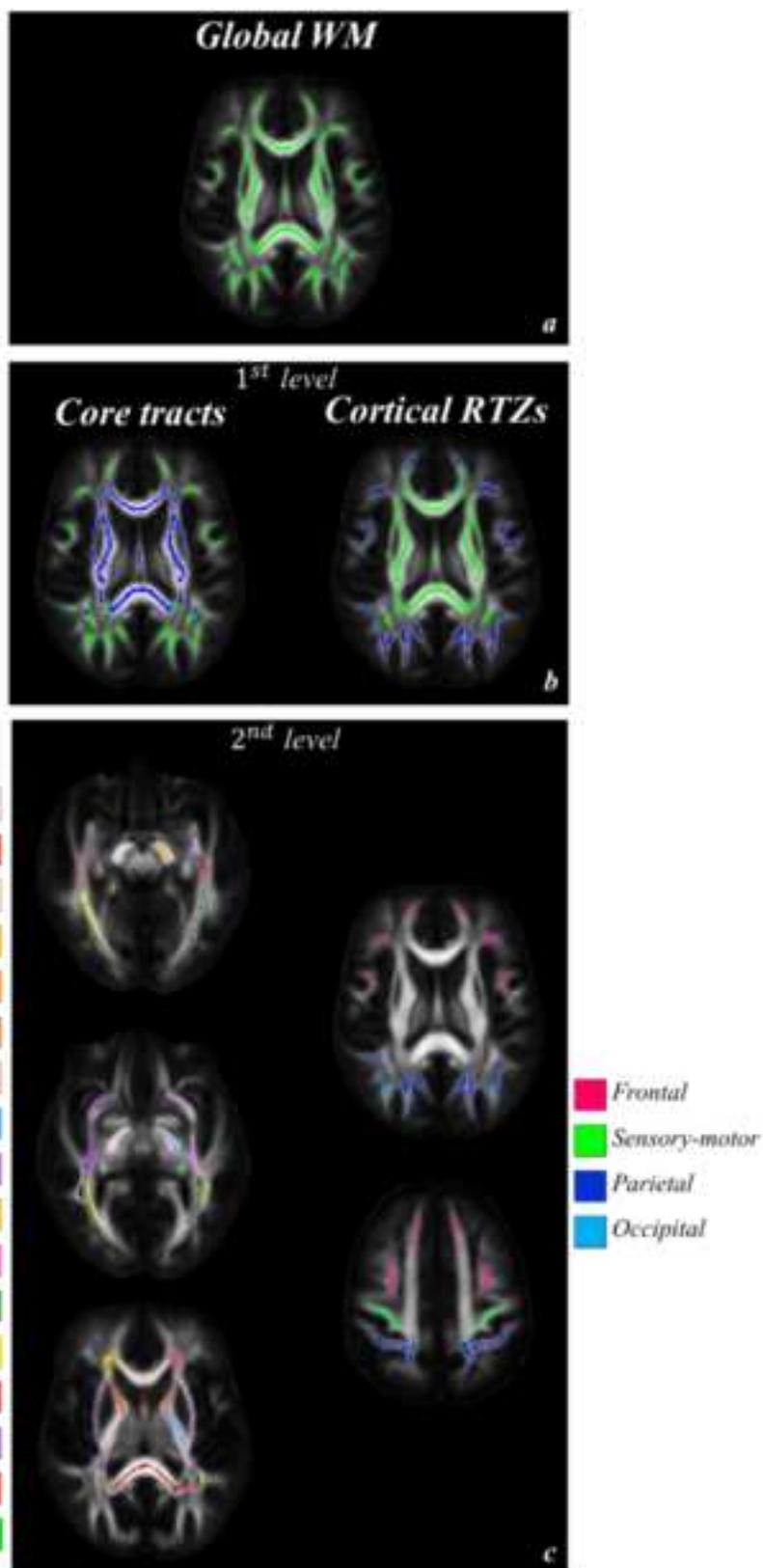Normalization and projection of the other parametric maps
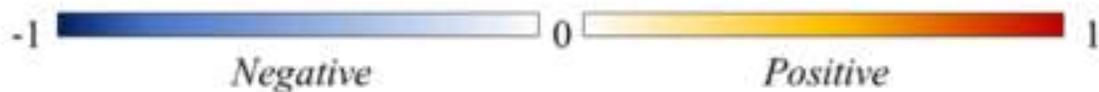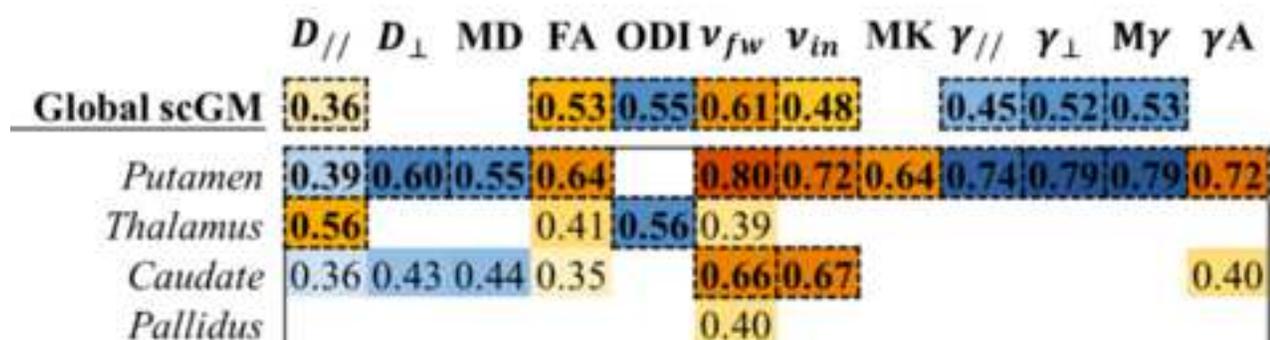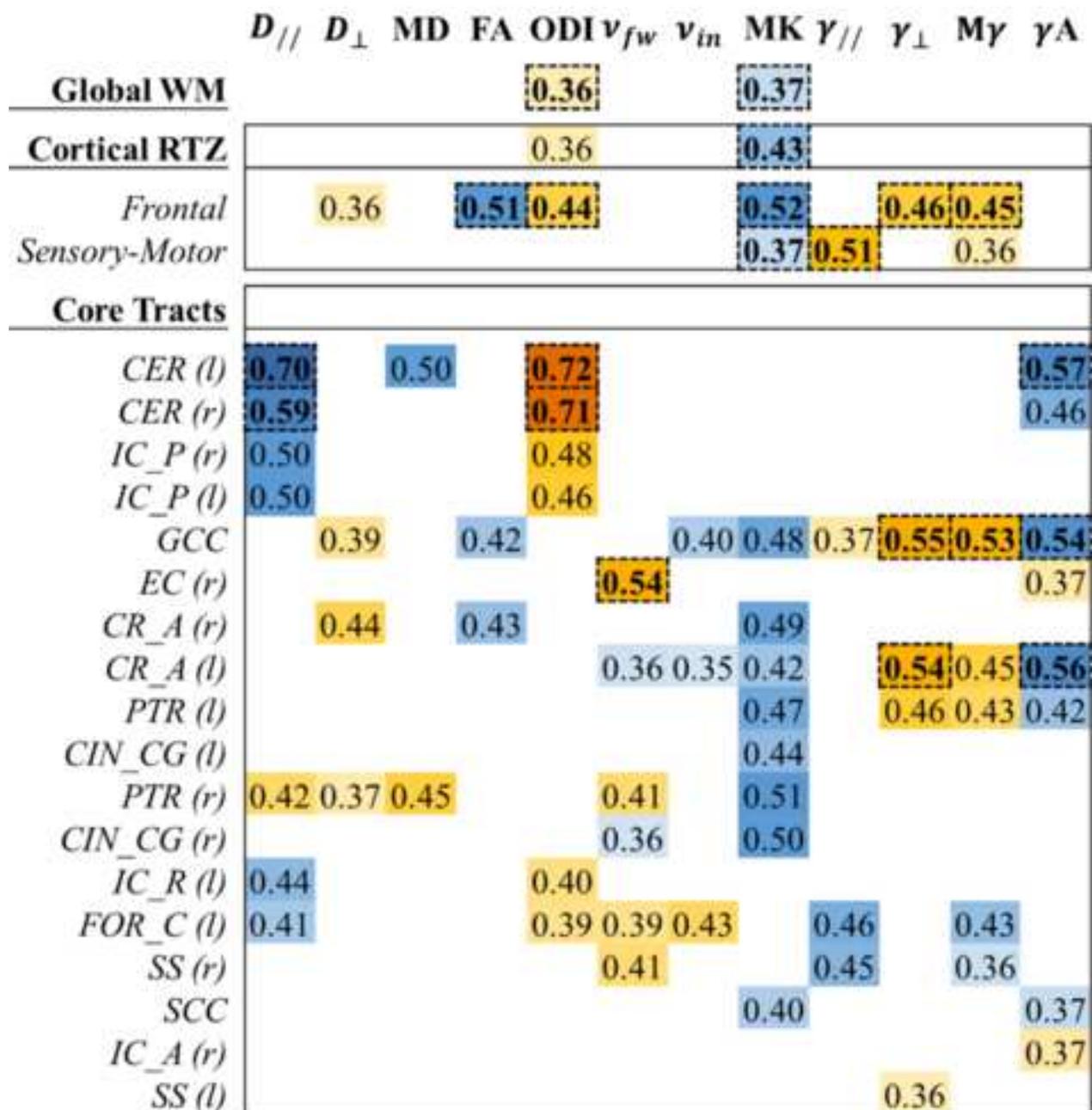*ROI-based analysis*   *Voxel-wise analysis*

Global WM

1st level
Core tracts
Cortical RTZs

2nd level

Genu of corpus callosum (GCC)
Splenium of corpus callosum (SCC)
Cerebral peduncle R (CER_r)
Cerebral peduncle L (CER_l)
Anterior limb of internal capsule R (IC_A_r)
Anterior limb of internal capsule L (IC_A_l)
Posterior limb of internal capsule R (IC_P_r)
Posterior limb of internal capsule L (IC_P_l)
Retrolenticular part of internal capsule L (IC_R_l)
Anterior corona radiata R (CR_A_r)
Anterior corona radiata L (CR_A_l)
Posterior thalamic radiation R (PTR_r)
Posterior thalamic radiation L (PTR_l)
Sagittal stratum L (SS_l)
External capsule R (EC_r)
Cingulate gyrus L (CIN_CG_l)
Fornix Stria terminalis L (FOR_C_l)

Frontal
Sensory-motor
Parietal
Occipital

	$D_{\parallel}$	$D_{\perp}$	MD	FA	ODI	v_{fw}	v_{in}	MK	$\gamma_{\parallel}$	$\gamma_{\perp}$	$M\gamma$	γA
Global WM					0.36			0.37				
Cortical RTZ					0.36			0.43				
Frontal	0.36			0.51	0.44			0.52		0.46	0.45	
Sensory-Motor								0.37	0.51		0.36	
Core Tracts												
CER (l)	0.70		0.50	0.72								0.57
CER (r)	0.59			0.71								0.46
IC_P (r)	0.50			0.48								
IC_P (l)	0.50			0.46								
GCC		0.39		0.42		0.40	0.48	0.37	0.55	0.53	0.54	
EC (r)					0.54							0.37
CR_A (r)		0.44		0.43				0.49				
CR_A (l)						0.36	0.35	0.42	0.54	0.45	0.56	
PTR (l)								0.47	0.46	0.43	0.42	
CIN_CG (l)								0.44				
PTR (r)	0.42	0.37	0.45		0.41			0.51				
CIN_CG (r)					0.36			0.50				
IC_R (l)	0.44				0.40							
FOR_C (l)	0.41				0.39	0.39	0.43		0.46		0.43	
SS (r)						0.41			0.45		0.36	
SCC								0.40				0.37
IC_A (r)												0.37
SS (l)										0.36		

	$D_{\parallel}$	$D_{\perp}$	MD	FA	ODI	v_{fw}	v_{in}	MK	$\gamma_{\parallel}$	$\gamma_{\perp}$	$M\gamma$	γA
Global scGM	0.36			0.53	0.55	0.61	0.48		0.45	0.52	0.53	
Putamen	0.39	0.60	0.55	0.64		0.80	0.72	0.64	0.74	0.79	0.79	0.72
Thalamus	0.56				0.41	0.56	0.39					
Caudate	0.36	0.43	0.44	0.35		0.66	0.67				0.40	
Pallidus						0.40						

-1 ———— 0 ————— 1

Negative   *Positive*

10. Supplementary Material

Click here to download 10. Supplementary Material: SupplementaryMaterials.docx

Resource data for this article

The data belongs to a larger research project and we are not allowed to share it.

We are happy to share the code for our γ-weighted maps on demand.