



**HAL**  
open science

## Age-related changes of Peak width Skeletonized Mean Diffusivity (PSMD) across the adult life span: a multi-cohort study

Grégory Beaudet, Ami Tsuchida, Laurent Petit, Christophe Tzourio, Jan Schreiber, Zdenka Pausova, Yash Patel, Tomas Paus, Lukas Pirpamer, Perminder S Sachdev, et al.

### ► To cite this version:

Grégory Beaudet, Ami Tsuchida, Laurent Petit, Christophe Tzourio, Jan Schreiber, et al.. Age-related changes of Peak width Skeletonized Mean Diffusivity (PSMD) across the adult life span: a multi-cohort study. 2020. hal-03007022

**HAL Id: hal-03007022**

**<https://hal.science/hal-03007022>**

Preprint submitted on 16 Nov 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Age-related changes of Peak width Skeletonized Mean Diffusivity (PSMD) across the adult life span: a multi-cohort study

1 Grégory Beaudet<sup>1</sup>, Ami Tsuchida<sup>1</sup>, Laurent Petit<sup>1</sup>, Christophe Tzourio<sup>2</sup>, Svenja  
2 Caspers<sup>3, 4</sup>, Jan Schreiber<sup>3</sup>, Zdenka Pausova<sup>5</sup>, Yash Patel<sup>5</sup>, Tomas Paus<sup>6</sup>, Reinhold  
3 Schmidt<sup>7</sup>, Lukas Pirpamer<sup>7</sup>, Perminder S. Sachdev<sup>8</sup>, Henry Brodathy<sup>8</sup>, Nicole Kochan<sup>8</sup>,  
4 Julian Trollor<sup>8</sup>, Wei Wen<sup>8</sup>, Nicola J. Armstrong<sup>9</sup>, Ian J. Deary<sup>10</sup>, Mark E. Bastin<sup>10,11</sup>,  
5 Joanna M. Wardlaw<sup>10,11</sup>, Susana Munõz Maniega<sup>10,11</sup>, A. Veronica Witte<sup>12</sup>, Arno  
6 Villringer<sup>12</sup>, Marco Duering<sup>13</sup>, Stéphanie Debette<sup>2,14</sup>, and Bernard Mazoyer<sup>1</sup>

7 <sup>1</sup>Institute of Neurodegenerative Diseases (IMN), CNRS, CEA, & University of Bordeaux,  
8 Bordeaux, France

9 <sup>2</sup>Bordeaux Population Health Research Center, Inserm U1219 & University of Bordeaux,  
10 Bordeaux, France

11 <sup>3</sup>Institute of Neuroscience and Medicine (INM-1), Research Centre Juelich, Juelich, Germany

12 <sup>4</sup>Institute for Anatomy I, Medical Faculty, Heinrich Heine University Dusseldorf, Dusseldorf,  
13 Germany

14 <sup>5</sup>The Hospital for Sick Children and Department of physiology and Nutritional Sciences,  
15 University of Toronto, Toronto, ON, Canada

16 <sup>6</sup>Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital and  
17 Departments of Psychology & Psychiatry, University of Toronto, Toronto, ON, Canada

18 <sup>7</sup>Department of Neurology, Medical University of Graz, Graz, Austria

19 <sup>8</sup>Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, UNSW Medicine, University  
20 of New South Wales, Sydney, NSW, Australia & Neuropsychiatric Institute Prince of Wales  
21 Hospital, Randwick, NSW, Australia

22 <sup>9</sup>Mathematics and Statistics, Murdoch University, Perth, WA, Australia

23 <sup>10</sup>Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology,  
24 University of Edinburgh, Edinburgh, United Kingdom

25 <sup>11</sup>Brain Research Imaging Centre, Division of Clinical Neurosciences, MRC Institute for  
26 Dementia Research, University of Edinburgh, Edinburgh, United Kingdom

27 <sup>12</sup>Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

28 <sup>13</sup>Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich,  
29 Munich, Germany

30 <sup>14</sup>Department of Neurology, Bordeaux University Hospital, Bordeaux, France

31

32 \* **Correspondence:**

33 Bernard Mazoyer

34 [bernard.mazoyer@u-bordeaux.fr](mailto:bernard.mazoyer@u-bordeaux.fr)

35 **Keywords: ageing, white matter, neurodegeneration, MRI, diffusion, PSMD**

36

37 **Abstract**

38 Parameters of water diffusion in white matter derived from diffusion-weighted imaging (DWI),  
39 such as fractional anisotropy (FA), mean, axial, and radial diffusivity (MD, AD and RD), and  
40 more recently, peak width of skeletonized mean diffusivity (PSMD), have been proposed as  
41 potential markers of normal and pathological brain ageing. However, their relative evolution  
42 over the entire adult lifespan in healthy individuals remains partly unknown during early and  
43 late adulthood, and particularly for the PSMD index. Here, we gathered and meta-analyzed  
44 cross-sectional diffusion tensor imaging (DTI) data from 10 population-based cohort studies  
45 in order to establish the time course of white matter water diffusion phenotypes from post-  
46 adolescence to late adulthood. DTI data were obtained from a total of 20,005 individuals aged  
47 18.1 to 92.6 years and analyzed with the same pipeline for computing DTI metrics. For each  
48 individual MD, AD, RD, and FA mean values were computed over their FA volume skeleton,  
49 PSMD being calculated as the 90% peak width of the MD values distribution across the FA

50 skeleton. Mean values of each DTI metric were found to strongly vary across cohorts, most  
51 likely due to major differences in DWI acquisition protocols as well as pre-processing and DTI  
52 model fitting. However, age effects on each DTI metric were found to be highly consistent  
53 across cohorts. RD, MD and AD variations with age exhibited the same U-shape pattern, first  
54 slowly decreasing during post-adolescence until the age of 30, 40 and 50, respectively, then  
55 progressively increasing until late life. FA showed a reverse profile, initially increasing then  
56 continuously decreasing, slowly until the 70's, then sharply declining thereafter. By contrast,  
57 PSMD constantly increased, first slowly until the 60's, then more sharply. These results  
58 demonstrate that, in the general population, age affects PSMD in a manner different from that  
59 of other DTI metrics. The constant increase in PSMD throughout the entire adult life, including  
60 during post-adolescence, indicates that PSMD could be an early marker of the ageing  
61 process.

## 62 **1 Introduction**

63 Parameters of water diffusion in white matter derived from diffusion-weighted imaging (DWI),  
64 such as fractional anisotropy (FA), mean, axial, and radial diffusivity (MD, AD and RD) are  
65 well-established markers of normal brain maturation(1)(2)(3)(4)(5) and ageing  
66 (6)(7)(8)(9)(10)(11)(12) and have been proposed as potential tools for the investigation of  
67 various brain disorders (13)(14)(15)(16)(17)(18)(19).

68 More recently, peak width of skeletonized mean diffusivity (PSMD, (20)), a new phenotype of  
69 white matter microstructure that can be derived from DWI, has been proposed as an imaging  
70 biomarker of small vessel disease (SVD, (20)(21)) and a correlate of cognitive impairment,  
71 particularly processing speed (20)(22)(21). So far, our knowledge of the PSMD distribution in  
72 healthy individuals has been limited to these three previously mentioned studies that all  
73 included people aged over 50 years. In addition, none of these studies addressed the issue  
74 of changes in PSMD across lifespan, which is critical for establishing whether PSMD could  
75 be used as an imaging marker of brain aging as well as an early predictor of age-related  
76 disorders or to serve as a tool to monitor outcomes in clinical trials. Here, we gathered and  
77 meta-analyzed cross-sectional diffusion tensor imaging (DTI) data from 10 population-based  
78 cohort studies in order to establish the time course, from post-adolescence to late adulthood,  
79 of the PSMD distribution and compare it with that of more commonly used white matter water  
80 diffusion phenotypes in white matter.

## 81 **2 Materials and Methods**

### 82 **2.1 Participants**

83 Ten independent datasets coming from cross-sectional cohort studies were gathered in the  
84 present study, namely MRi-Share, BIL&GIN, SYS, LIFE-Adult, 1000 BRAINS, UKBiobank,  
85 ASPSF, OATS, LBC1936, MAS; (see acronym definition in Table 1 caption). All but three  
86 (LIFE-Adult, 1000BRAINS, and UKBiobank) were part of the BRIDGET Consortium (BRain  
87 Imaging, cognition, Dementia and next generation GEnomics: a Transdisciplinary approach  
88 to search for risk and protective factors of neurodegenerative disease), supported by EU-  
89 JPND (European Union Joint Programme – Neurodegenerative Disease Research). The 10  
90 datasets included a total of 20,005 individuals (age range: 18.1 to 92.6 years, 10,807 women  
91 and 9,198 men). Tables 1 and 2 detail sample size and age distribution for the 10 cohorts that  
92 were all of cross.

### 93 **2.2 Diffusion-weighted image acquisition and preprocessing**

94 Tables 3 and 4 summarize the main characteristics of the DWI acquisition and preprocessing  
95 for the 10 cohorts. Overall, there was considerable variability between studies regarding  
96 almost all acquisition parameters, including scanner manufacturer, field strength, gradient  
97 strength, diffusion pulse sequence, resolution and number of directions. For the present work,  
98 it was not possible to access raw DWI data at different sites in order to harmonize processing  
99 from the initial DICOM data. For this reason, DWI datasets were pre-processed with  
100 procedures specific to each site, including exclusion of data upon visual detection of major  
101 artifacts due to eddy current distortions or head motion. AD, RD, MD and FA maps were  
102 computed by fitting the DTI model parameters in each voxel from these preprocessed DWI  
103 volumes. Additional details on DWI preprocessing and DTI parameter map computation for  
104 each dataset are provided in the Supplementary Material section.

### 105 **2.3 Derivation of DTI metrics**

106 Various metrics were derived from the DTI data using a script developed by Baykara et al.  
107 (<http://www.psm-d-marker.com>, (20)). This original script was designed to extract PSMD, an  
108 index of the dispersion of MD values across the white matter skeleton. Briefly, the  
109 computation included two steps: 1-WM skeletonizing using the FA map, and 2- analyzing the

110 voxel value distribution histogram in the MD volume masked by the WM-FA skeleton. The FA  
111 volume of each individual was skeletonized using the FSL-TBSS software, part of the FMRIB  
112 Software Library (FSL) (23)(24), using the FMRIB 1mm FA template and applying a 0.2  
113 threshold on FA maps. Then the MD volume of the same individual was masked, keeping  
114 only voxels within the FA skeleton. Furthermore, in order to reduce contamination of the  
115 skeleton by CSF voxels, the FA-masked MD volumes were further masked by both a standard  
116 FA skeleton with a threshold of 0.3 on FA values and a custom mask (provided with the PSMD  
117 software tool) designed so as to exclude regions adjacent to the ventricles, such as the fornix.  
118 Finally, PSMD was computed as the difference between the 95<sup>th</sup> and 5<sup>th</sup> percentiles of the so-  
119 masked MD volume voxel value distribution. Here, we extended this script in order to obtain,  
120 in addition to PSMD values, estimates of the mean values of axial, radial, and mean diffusivity  
121 (AD, RD, MD, respectively) as well as of fractional anisotropy (FA) over the same customized  
122 skeleton. All 10 cohorts were processed separately with this customized script and the results  
123 sent to the Bordeaux site where they were combined for further statistical analysis.

## 124 **2.4 Statistical analyses**

### 125 **2.4.1 Age category definition**

126 Due to previously reported non-linear effects of age on DTI metrics (1)(3)(8), we divided each  
127 cohort sample into subsamples of 10-years age range starting at 18 years of age, the last  
128 subsample (i.e. [78 to 98]) including all subjects aged over 78 years, as there was only a small  
129 number of individuals aged over 88 years. Table 1 and Figure 1 detail the contribution of each  
130 cohort to each age category. Because we planned running analyses at the age category by  
131 cohort by sex level, we discarded subsamples of small sizes, namely containing less than 30  
132 individuals.

### 133 **2.4.2 Assessing age-related changes of PSMD and other DTI metrics**

134 For each of the five DTI metrics and each age category, we performed an analysis of variance  
135 including “Age” as the main effect, and “Sex”, “TIV” (total intracranial volume), and “Cohort”  
136 as confounding factors. The Cohort effect was included in order to account for apparent large  
137 differences in DTI metric average values across cohorts contributing to the same age  
138 category dataset (see Figure 2). In order to document differences of age effects between  
139 cohorts contributing to the same age category, we also performed an analysis of variance for

140 each age category and each cohort, including “Age”, “Sex” and “TIV” as effects. Moreover,  
141 we analyzed the effects of age on DTI metrics in men and women separately.

### 142 **2.4.3 Assessing the effects of Sex and TIV on PSMD and other DTI metrics**

143 For each of the five DTI metrics and each age category, we also performed an analysis of  
144 variance including “Sex” and “TIV” as main factors and “Cohort” as confounding factors.

145 All statistical analyses were performed using the JMP Pro Software (version 14.3.0, SAS  
146 Institute Inc.).

## 147 **3 Results**

### 148 **3.1 Descriptive statistics**

149 Tables 3a to 3e provide basic statistics across age categories and cohorts for PSMD and the  
150 four other DTI metrics, while Figure 2 illustrates their respective profiles across the adult  
151 lifespan. From both Table 3 and Figure 2 it is apparent that there is considerable variability in  
152 all five DTI parameter values, and that within a given age category the variability across  
153 cohorts is larger than the variability between individuals of the same cohort (see the extreme  
154 case of AD and FA values for the LBC1936 study performed at 1.5T, for example).

155 Figure 3 compares the inter-individual variability of PSMD (in terms of its coefficient of  
156 variation, CV in %) within each cohort to those of the other DTI metrics, again for each age  
157 category and each cohort, revealing that PSMD CV's is in the order of 10 to 15% (with values  
158 as high as 20% for later ages) while those for AD, RD, MD and FA are in the order of 2 to 5%.  
159 Note also that the CV's of all DTI metrics increase with age, more for PSMD than for the other  
160 parameters.

### 161 **3.2 Effects of age on PSMD and other DTI metrics**

162 The evolution of PSMD across the adult life is different from that of the other metrics (Figure  
163 2). Indeed, PSMD seems to increase monotonically with age whereas AD, RD, and MD exhibit  
164 a similar J-shape profile, initially slightly decreasing during post-adolescence before later  
165 increasing during adulthood. As for FA, it shows a reverse profile to that of AD, RD and MD,  
166 with an initial small increase followed by a later decrease.

167 This apparent specific lifespan profile of PSMD was confirmed by the quantitative estimates  
168 of the effects of age on PSMD and other DTI metrics provided by the between-cohort ANOVA  
169 (see Table 4) and their profiles of evolution across age categories as shown in Figure 4.  
170 Estimates of the age effect on PSMD were indeed positive for all age categories and  
171 significant for all but the [28 to 38] age period. This increase in PSMD accelerated during late  
172 life periods, its value being multiplied by a factor of 3 between the [58 to 68] and the [78 to  
173 98] periods. By contrast, AD, RD, and MD age variation profiles were characterized by an  
174 initial small but significant decrease (negative age effect), followed by a stable period (non-  
175 significant age effect) and a final significant increase (positive age effect). What distinguished  
176 AD, RD and MD profiles was their respective timings, the initial decrease in RD and MD being  
177 significant only for the [18 to 28] subsample, while it extended over the [38 to 48] period for  
178 AD. Note that since the stable period covered two periods of 10 years for all three metrics,  
179 the increase in AD was delayed by 10 years compared with RD and MD. At the same time,  
180 FA exhibited the reverse contrast consisting of an initial increase during the [18 to 28] period  
181 followed by a stable period ([28 to 38]) before an accelerated decrease during the rest of the  
182 adult life course. The age effects on DTI metrics were not significantly different between men  
183 and women as revealed by the separate sex-specific analyses of age effects.

### 184 **3.3 Effects of Sex and TIV on DTI**

185 Amplitude of sex effects on DTI metric average values were found to be quite variable across  
186 the various cohorts for the different age categories (see Figure 5). When pooling all datasets,  
187 we found that sex had significant effects on all DTI parameters except on FA. Women had  
188 higher mean AD and MD values than men, who conversely had higher PSMD values than  
189 women (see Table 5). As for TIV, we found that it had positive effects on all DTI parameters  
190 (see Table 5), including PSMD, these effects being very significant ( $p < 10^{-4}$ ) in all cases but  
191 RD ( $p=0.53$ ).

## 192 **4 Discussion**

193 We will first discuss methodological issues and potential limitations in interpreting results of  
194 our study. Second, we will discuss what the present study adds to the already existing  
195 literature on age effects on classical DTI parameters. In the third part, we will focus on the  
196 original findings regarding PSMD distribution and evolution over the adult life.



#### 197 **4.1 Methodological issues and potential limitations of the present study**

198 In order to study the effects of age over the entire adult lifespan, we gathered DTI data from  
199 20,005 individuals scanned at 10 different sites with the major objective of maximizing  
200 statistical power. By so doing, we were aware that the variability of DTI parameters derived  
201 from the entire dataset would be much larger than for a single site study because of between-  
202 site differences in data acquisition protocols such as scanner manufacturer, field strength,  
203 number and strength of diffusion-encoding gradients, image voxel size, and post-processing  
204 of raw DWI data, and so on (23)(24)(25)(26)(27)(28). Accordingly, a key issue was to reduce  
205 as much as possible the variability due to sources that were controllable so that we could  
206 maximize benefits of the very large sample size.

207 Concerns with DTI data meta-analysis have been emphasized by several authors (29)(30)  
208 and strategies have been proposed for harmonizing DWI data before proceeding to statistical  
209 analysis of DTI parameter maps. However, it has also been reported that DTI parameters  
210 estimated over the whole white matter or large regions of interest actually exhibit high intra-  
211 and inter-scanner reproducibility, making them suitable for multisite studies without extensive  
212 harmonization (17)(31)(32). This is the approach that we implemented here as it was not  
213 possible to access raw DWI data at different sites in order to harmonize processing from the  
214 very earliest stages (see Supplementary Materials). In our study, harmonization was limited  
215 to the post-processing of DTI maps pre-computed by each site using the same script for  
216 generating individual skeletons and computing individual DTI parameter values across these  
217 skeletons. However, our findings indicate that it is possible to draw meaningful conclusions  
218 from such minimal harmonization by focusing on the effects of interest (age in our case) rather  
219 than the absolute values of the measurements, an approach previously used by others (33).

220 Multi-site studies do have some advantages as compared with single-site investigations,  
221 namely statistical power due to very large sample size, and the ability to recruit a sufficient  
222 number of individuals over the entire life or adult lifespan. As emphasized by others, these  
223 are important features in the context of clinical studies that are often multisite in nature  
224 (17)(31). In fact, there have been several previous reports of multisite studies on DTI  
225 parameters in adults but they dealt with issues other than age effects such as methodology  
226 (26)(17)(29) and genetic effects (34)(35), for example.

227 In this study, we focused on the mean DTI metrics over a white matter skeleton, rather than  
228 over the entire white-matter compartment, since our primary metric of interest was PSMD,  
229 which is defined over the FSL-TBSS white matter skeleton derived from FA data. This  
230 approach should in theory minimize any partial volume effects by limiting the measurement  
231 over the core of white matter tracts. Indeed, when we compared the mean DTI metrics over  
232 the white matter skeleton with those measured over the whole white-matter compartment in  
233 two cohorts of the study (MRi-Share and BIL&GIN), mean FA values were higher and  
234 diffusivity values lower when averaged over the white matter skeleton than when averaged  
235 over the entire white-matter compartment. However, the cross-subject variability measured  
236 as the CV of the mean DTI metrics decreased only marginally (a fraction of a percent for CVs  
237 ranging from 2% to 4%) when mean values were computed over the white matter skeleton  
238 rather than the whole white matter. In contrast, the CV of PSMD decreased markedly (on  
239 average from 24% to 8%) when its computation was performed on the white matter skeleton  
240 rather than on the global white-matter mask. This demonstrates the importance of  
241 choosing a measure of MD dispersion values over a white matter skeleton for controlling  
242 between subject variability.

243 In the present work, we restricted the analysis to classical DTI metrics as only two of the  
244 contributing cohorts had high angular resolution and/or multi-shell acquisition schemes that  
245 could be used for estimating advanced white-matter microstructural parameters with more  
246 sophisticated models (25). Here, DWI data processing was solely based on the classical DTI  
247 model. The DTI model limitations are well-known (24) and it has been shown, for example,  
248 that correction for free water has a major impact on classical DTI parameter values (36)(37).  
249 However, although investigating advanced white-matter microstructural parameters is highly  
250 desirable, it was beyond the scope of our study: it would require additional datasets with multi-  
251 shell acquisition, especially for individuals aged 30 to 50 years or over 70 years, in order to  
252 supplement existing data (8) on the adult lifespan trajectory of these microstructural  
253 parameters.

254 We included “Sex” and “TIV” as covariates in our statistical analyses. Mixed results have been  
255 reported regarding the impact of sex on DTI measures ((38)(39)(40)(12)(41), see review in  
256 (3)). Here we also observed mixed results across the different cohorts, although very  
257 significant sex effects on all DTI parameters, except FA, were uncovered when combining the

258 entire dataset. Note, however, these sex effects were of very small size (for PSMD, for  
259 example,  $\omega^2=6.7 \times 10^{-3}$  for the sex effect to be compared with  $7.6 \times 10^{-2}$  for the age effect),  
260 which could explain the mixed findings in the literature, and suggests further investigations  
261 are required in order to understand their biological origins. TIV effects on DTI parameters are  
262 not well established in the literature. In our study, we found that TIV was positively correlated  
263 with all DTI parameters except for RD. Similar to sex, TIV effects when significant were very  
264 small (for PSMD again,  $\omega^2=1.5 \times 10^{-3}$  for the TIV effect). Here again additional  
265 investigations are needed to understand the origins of these effects.

266 Finally, and importantly, it should be stressed that interpretation of the results of the present  
267 study should be taken with caution because of the cross-sectional nature of the data that we  
268 analyzed. Numerous reports have indeed pointed out the caveats of cross-sectional design  
269 for assessing effects of age and demonstrated how such design may lead to spurious findings  
270 when compared to those obtained with longitudinal data ((12)(42)(43)). In the present work,  
271 there was no attempt to use a single model to describe the variation of DTI parameters with  
272 age over the entire adulthood period. Rather, we selected a piecewise linear model to  
273 examine/compare age-related changes in 10-year duration consecutive time bins, thereby  
274 minimizing the generation bias between cohorts of nearby categories. Understandably, such  
275 an approach does not eradicate the intrinsic limits of our cross-sectional study. But it should  
276 be reminded that a fully longitudinal design is quasi impossible to implement in the context of  
277 lifespan research, since, in practice, measures in an individual can be repeated only a few  
278 times and at short duration intervals. As a consequence, such longitudinal studies suffer from  
279 some of the limitations of cross-sectional ones. This may explain why the results of the  
280 present study are compatible with those a previously published longitudinal study (12) in  
281 which individuals aged between 20 and 84 years were observed twice 3 years apart.

## 282 **4.2 Adult life span profiles of variation of classical DTI parameters AD, RD, MD and** 283 **FA**

284 Effects of age on white-matter microstructure assessed with DTI have been intensively  
285 investigated over the past decade from a developmental perspective (4) as well as in a  
286 lifespan/ageing framework (1)(11)(40)(3)(12)(11)(5)(8)(36). Briefly, and considering only DTI  
287 metrics estimated at the global level, AD, RD and thus MD were reported to follow similar U-  
288 or better J-shape age variation patterns, initially decreasing during childhood and

289 adolescence (see (4) for review) then exhibiting an accelerated increase during the adult life  
290 (12)(8), while FA followed a reverse profile. Our own findings agree with this body of results  
291 during the adult life course. Raw data plots show J-shape profiles for AD, RD and MD, and  
292 the reverse profile for FA, as well as acceleration of these changes during late life.

293 Maximum global FA values and minimum global MD, RD, and AD values have been reported  
294 to occur before the age of 40 (1)(40)(11)(5)(12), although large variations were found when  
295 considering individual tracts (44)(39)(45)(5). Here, we found extreme values for RD, MD and  
296 FA occurring between 28 and 38 years, well in line with these previous findings. In addition,  
297 we found that the decrease of AD in the post-adolescence period extended into adulthood by  
298 about 10 years more than for RD and MD, thereby uncovering heterochrony of AD and RD  
299 variations during adulthood. Such a heterochrony during adulthood was not detected in a  
300 previous longitudinal study (12) possibly due to an insufficient sample size and large DTI  
301 metric variability between individuals (as can be seen in Fig. 7 of the mentioned report). Note  
302 that two recent studies (46)(47) have reported opposite age effects for AD (decrease) and  
303 RD (increase) with stable MD during the 18 to 55 year age period; however, as both studies  
304 used simple linear modeling due to small sample sizes, no age at extreme value could be  
305 observed. Rather, our findings are compatible with the AD-RD variation heterochrony that has  
306 been noticed earlier during childhood and adolescence at the individual tract level with  
307 stronger decrease for RD than for AD (44)(30). According to these and our findings, the AD  
308 decrease / RD increase profile (6) would occur only during mid-adulthood.

### 309 **4.3 PSMD is a diffusion imaging phenotype with a profile of variation across the adult** 310 **life span that differs from that of other DTI parameters**

311 The distribution of PSMD values observed for the different cohorts and age categories of the  
312 present study are consistent with the few comparable data reported in the literature for older  
313 participants (no data are available in young adults). For example, Baykara et al. reported in  
314 their pioneering article a PSMD median value around 3.0 (in  $\text{mm}^2\text{s}^{-1} \times 10^{-4}$ , range [2.5, 4.9])  
315 in a sample of healthy individuals aged 60 to 80 years drawn from the ASPF cohort (see Table  
316 2 of Baykara et al (20)), values that are comparable to those reported in Table 3d of our study  
317 in subsamples of other cohorts of similar age category. Similarly, Wei et al (21) recently  
318 reported a PSMD average value of  $2.4 \times 10^{-4} \text{mm}^2\text{s}^{-1}$  in a sample of healthy controls aged  
319 around 60 years. In both studies, PSMD CVs were close to 10%, a value again similar to

320 those observed in our own study. That the CV of PSMD is 2 to 3 times larger than the CVs of  
321 other DTI metrics could be expected since PSMD is a dispersion rather than a central  
322 tendency statistic. Moreover, the larger increase in PSMD CV as age advances (as compared  
323 to the other DTI metrics) indicates that this phenotype should be used with caution especially  
324 during the late life period. However, it is important to note that the CV of PSMD was found to  
325 be quite stable across cohorts with similar age ranges.

326 The main goal of the present study was to document the profile of PSMD evolution across  
327 age bands during adulthood. In this respect, and the proviso that the data we gathered were  
328 not longitudinal, our results show that PSMD increases continuously from post-adolescence  
329 to late adult life, that this increase is accelerating at later ages, and that this acceleration is  
330 larger than for the other DTI metrics. As there are no available data of PSMD in childhood  
331 and adolescence, it is not possible to decide whether the lifetime PSMD evolution profile is  
332 similar to those of AD, RD, MD, i.e. with a decrease during childhood that reaches the  
333 minimum value before adulthood, or if it shows continuous increase throughout the lifespan.  
334 Nevertheless, it remains the case that the continuous and accelerating increase of PSMD  
335 during adulthood is an indication that it is an adequate and potentially valuable marker of  
336 white matter ageing. In particular, it is notable that PSMD increases during early adulthood  
337 when the other DTI metrics variations appear to be still undergoing late maturational  
338 processes.

339 The biological mechanisms of the origin of PSMD evolution with age are at present unknown,  
340 but one can think of several reasons why PSMD may be more prone to increase with age as  
341 compared with the other metrics. First, it is important to remember that PSMD is a measure  
342 of MD values dispersion across a skeleton of white matter. As such, it will be directly affected  
343 by differences across MD values of the individual tracts. Consequently, regional  
344 heterogeneity as well as heterochrony in MD values of the fiber tracts will result in higher  
345 PSMD values more than in average MD values. Second, MD itself is a weighted average of  
346 AD (1/3) and RD (2/3) values, and thus MD value dispersion will also be affected by  
347 heterochrony in AD and RD variations with age. Overall, what possibly makes PSMD an early  
348 and sensitive imaging marker of ageing is that it captures multiple sources of heterogeneity  
349 in white matter water diffusion parameters. With this regard, it would be interesting to  
350 investigate variations in the pattern of MD dispersion at the regional level using tract-based

351 DTI metrics since it is well established that heterochrony is a major feature of the development  
352 and aging of the different fiber tracts (see for example (44)(39)(8)(5)). Accordingly, variations  
353 of PSMD value provide only a gross and possibly biased estimate of the white matter-  
354 microstructure dynamics. We did not implement regional analysis as our study focused on  
355 PSMD that is by definition a dispersion statistic over the entire white matter skeleton.  
356 Nevertheless, a regional approach would certainly be interesting and feasible since peak  
357 width of MD values could be measured on a white-matter skeleton at the tract level in the  
358 same manner as it has been done for other DTI metrics (see (30)(46) for example).

## 359 **5 Acknowledgments**

360 Gregory Beaudet has been supported by an EU-ERC starting grant (SEGWAY, PI S Debette,  
361 with funding from the European Union's Horizon 2020 research and innovation program under  
362 grant agreement No 640643). Ami Tsuchida is supported by a grant from the Fondation pour  
363 la Recherche Médicale (DIC202161236446). Svenja Caspers was supported by the Initiative  
364 and Networking Fund of the Helmholtz Association and the European Union's Horizon 2020  
365 Research and Innovation Program under Grant Agreement 785907 (Human Brain Project  
366 SGA2). The BRIDGET project is supported by the Fondation Leducq (Transatlantic Network  
367 of Excellence on the Pathogenesis of SVD of the Brain) and is an EU Joint Program -  
368 Neurodegenerative Disease Research (JPND) project. The project is supported through the  
369 following funding organizations under the aegis of JPND -[www.jpnd.eu](http://www.jpnd.eu): Australia, National  
370 Health and Medical Research Council, Austria, Federal Ministry of Science, Research and  
371 Economy; Canada, Canadian Institutes of Health Research; France, French National  
372 Research Agency; Germany, Federal Ministry of Education and Research; Netherlands, The  
373 Netherlands Organization for Health Research and Development; United Kingdom, Medical  
374 Research Council. This project has received funding from the European Union's Horizon 2020  
375 research and innovation program under grant agreement No 643417. This project has also  
376 received funding from the European Research Council (ERC) under the European Union's  
377 Horizon 2020 research and innovation program under grant agreement No 640643.

## 378 **6 Author Contributions**

379 Study conception (BM, SD), data collection (GB, CT, SC, ZP, TP, RS, PS, HB, NK, JT, ID,  
380 VW, AV, BM), data analysis (GB, LP, SC, JS, YP, LP, PS, WW, NA, MB, SMM, VW, MD,

381 BM), drafting (GB, AT, BM), revising the manuscript (LP, CT, SC, JS, ZP, YP, TP, R, LP, PS,  
382 WW, NA, ID, MB, JW, SMM, VW, AV, MD, SD, BM).

## 383 **7 References**

384 1. Hasan KM, Sankar A, Halphen C, Kramer LA, Brandt ME, Juranek J, Cirino PT,  
385 Fletcher JM, Papanicolaou AC, Ewing-Cobbs L. Development and organization of the human  
386 brain tissue compartments across the lifespan using diffusion tensor imaging. *Neuroreport*  
387 (2007) **18**:1735-1739.

388 2. Giorgio A, Watkins KE, Chadwick M, James S, Winmill L, Douaud G, De Stefano N,  
389 Matthews PM, Smith SM, Johansen-Berg H, et al. Longitudinal changes in grey and white  
390 matter during adolescence. *NeuroImage* (2010) **49**:94–103.  
391 doi:10.1016/j.neuroimage.2009.08.003

392 3. Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C. Diffusion tensor imaging  
393 of white matter tract evolution over the lifespan. *NeuroImage* (2012) **60**:340–352.  
394 doi:10.1016/j.neuroimage.2011.11.094

395 4. Lebel C, Treit S, Beaulieu C. A review of diffusion MRI of typical white matter  
396 development from early childhood to young adulthood. *NMR Biomed* (2019) **32**:e3778.  
397 doi:10.1002/nbm.3778

398 5. Yeatman JD, Wandell BA, Mezer AA. Lifespan maturation and degeneration of human  
399 brain white matter. *Nat Commun* (2014) **5**:4932. doi:10.1038/ncomms5932

400 6. Bennett IJ, Madden DJ, Vaidya CJ, Howard DV, Howard JH. Age-related differences  
401 in multiple measures of white matter integrity: A diffusion tensor imaging study of healthy  
402 aging. *Hum Brain Mapp* (2010) **31**:378-390. doi:10.1002/hbm.20872

403 7. Bartzokis G, Lu PH, Heydari P, Couvrette A, Lee GJ, Kalashyan G, Freeman F,  
404 Grinstead JW, Villablanca P, Finn JP, et al. Multimodal Magnetic Resonance Imaging  
405 Assessment of White Matter Aging Trajectories Over the Lifespan of Healthy Individuals. *Biol*  
406 *Psychiatry* (2012) **72**:1026–1034. doi:10.1016/j.biopsych.2012.07.010

407 8. Cox SR, Ritchie SJ, Tucker-Drob EM, Liewald DC, Hagenaars SP, Davies G, Wardlaw

- 408 JM, Gale CR, Bastin ME, Deary IJ. Ageing and brain white matter structure in 3,513 UK  
409 Biobank participants. *Nat Commun* (2016) **7**:13629. doi:10.1038/ncomms13629
- 410 9. de Lange A-MG, Bråthen ACS, Rohani DA, Fjell AM, Walhovd KB. The temporal  
411 dynamics of brain plasticity in aging. *Cereb Cort* (2018) **28**:1857-1865. doi:  
412 10.1093/cercor/bhy003
- 413 10. Rathee R, Rallabandi VPS, Roy PK. Age-related differences in white matter integrity  
414 in healthy human brain: evidence from structural MRI and diffusion tensor imaging. *Magn*  
415 *Reson Insights* (2016) **9**:9-20. doi:10.4137/MRI.S39666
- 416 11. Westlye LT, Walhovd KB, Dale AM, Bjornerud A, Due-Tonnessen P, Engvig A,  
417 Grydeland H, Tamnes CK, Ostby Y, Fjell AM. Life-Span Changes of the Human Brain White  
418 Matter: Diffusion Tensor Imaging (DTI) and Volumetry. *Cereb Cortex* (2010) **20**:2055–2068.  
419 doi:10.1093/cercor/bhp280
- 420 12. Sexton CE, Walhovd KB, Storsve AB, Tamnes CK, Westlye LT, Johansen-Berg H,  
421 Fjell AM. Accelerated Changes in White Matter Microstructure during Aging: A Longitudinal  
422 Diffusion Tensor Imaging Study. *J Neurosci* (2014) **34**:15425–15436.  
423 doi:10.1523/JNEUROSCI.0203-14.2014
- 424 13. for the Alzheimer’s Disease Neuroimaging Initiative, Chandra A, Dervenoulas G, Politis  
425 M. Magnetic resonance imaging in Alzheimer’s disease and mild cognitive impairment. *J*  
426 *Neurol* (2019) **266**:1293–1302. doi:10.1007/s00415-018-9016-3
- 427 14. Tae W-S, Ham B-J, Pyun S-B, Kang S-H, Kim B-J. Current clinical applications of  
428 diffusion-tensor imaging in neurological disorders. *J Clin Neurol* (2018) **14**:129.  
429 doi:10.3988/jcn.2018.14.2.129
- 430 15. Shen X, Adams MJ, Ritakari TE, Cox SR, McIntosh AM, Whalley HC. White matter  
431 microstructure and its relation to longitudinal measures of depressive symptoms in mid- and  
432 late life. *Biol Psychiatry* (2019) **86**:759-768. doi:10.1016/j.biopsych.2019.06.011
- 433 16. Suzuki H, Gao H, Bai W, Evangelou E, Glocker B, O’Regan DP, Elliott P, Matthews  
434 PM. Abnormal brain white matter microstructure is associated with both pre-hypertension and  
435 hypertension. *PLOS ONE* (2017) **12**:e0187600. doi:10.1371/journal.pone.0187600



- 436 17. Croall ID, Lohner V, Moynihan B, Khan U, Hassan A, O'Brien JT, Morris RG, Tozer  
437 DJ, Cambridge VC, Harkness K, et al. Using DTI to assess white matter microstructure in  
438 cerebral small vessel disease (SVD) in multicentre studies. *Clin Sci* (2017) **131**:1361–1373.  
439 doi:10.1042/CS20170146
- 440 18. Dekkers IA, Jansen PR, Lamb HJ. Obesity, Brain volume, and white matter  
441 microstructure at MRI: A Cross-sectional UK Biobank Study. *Radiology* (2019) **291**:763–771.  
442 doi:10.1148/radiol.2019181012
- 443 19. Zavaliangos-Petropulu A, Nir TM, Thomopoulos SI, Reid RI, Bernstein MA, Borowski  
444 B, Jack Jr. CR, Weiner MW, Jahanshad N, Thompson PM. Diffusion MRI Indices and their  
445 relation to cognitive impairment in brain aging: the updated multi-protocol approach in ADNI3.  
446 *Front Neuroinformatics* (2019) **13**:2. doi:10.3389/fninf.2019.00002
- 447 20. Baykara E, Gesierich B, Adam R, Tuladhar AM, Biesbroek JM, Koek HL, Ropele S,  
448 Jouvent E, Alzheimer's Disease Neuroimaging Initiative, Chabriat H, et al. a novel imaging  
449 marker for small vessel disease based on skeletonization of white matter tracts and diffusion  
450 histograms. *Ann Neurol* (2016) **80**:581–592. doi:10.1002/ana.24758
- 451 21. Wei N, Deng Y, Yao L, Jia W, Wang J, Shi Q, Chen H, Pan Y, Yan H, Zhang Y, et al.  
452 A Neuroimaging marker based on diffusion tensor imaging and cognitive impairment due to  
453 cerebral white matter lesions. *Front Neurol* (2019) **10**:81. doi:10.3389/fneur.2019.00081
- 454 22. Deary IJ, Ritchie SJ, Muñoz Maniega S, Cox SR, Valdés Hernández MC, Luciano M,  
455 Starr JM, Wardlaw JM, Bastin ME. Brain Peak Width of Skeletonized Mean Diffusivity (PSMD)  
456 and cognitive function in later life. *Front Psychiatry* (2019) **10**:524.  
457 doi:10.3389/fpsy.2019.00524
- 458 23. Barrio-Arranz G, de Luis-García R, Tristán-Vega A, Martín-Fernández M, Aja-  
459 Fernández S. Impact of MR acquisition parameters on DTI scalar indexes: a tractography  
460 based approach. *PLOS ONE* (2015) **10**:e0137905. doi:10.1371/journal.pone.0137905
- 461 24. Curran KM, Emsell L, Leemans A. "Quantitative DTI Measures," in *Diffusion Tensor*  
462 *Imaging*, eds. W. Van Hecke, L. Emsell, S. Sunaert (New York, NY: Springer New York), 65–  
463 87. doi:10.1007/978-1-4939-3118-7\_5

- 464 25. Alexander DC, Dyrby TB, Nilsson M, Zhang H. Imaging brain microstructure with  
465 diffusion MRI: practicality and applications. *NMR Biomed* (2019) **32**:e3841.  
466 doi:10.1002/nbm.3841
- 467 26. Helmer KG, Chou M-C, Preciado RI, Gimi B, Rollins NK, Song A, Turner J, Mori S.  
468 Multi-site study of diffusion metric variability: characterizing the effects of site, vendor, field  
469 strength, and echo time using the histogram distance. in *Proc SPIE Int Soc Opt Eng* (2016),  
470 eds. B. Gimi, A. Krol (San Diego, California, United States), 9788. doi:10.1117/12.2217449
- 471 27. Qin W, Shui Yu C, Zhang F, Du XY, Jiang H, Xia Yan Y, Cheng Li K. Effects of echo  
472 time on diffusion quantification of brain white matter at 1.5T and 3.0T. *Magn Reson Med*  
473 (2009) **61**:755–760. doi:10.1002/mrm.21920
- 474 28. Hutchinson EB, Avram AV, Irfanoglu MO, Koay CG, Barnett AS, Komlosh ME,  
475 Özarslan E, Schwerin SC, Juliano SL, Pierpaoli C. Analysis of the effects of noise, DWI  
476 sampling, and value of assumed parameters in diffusion MRI models: Cross-Model Analysis  
477 of Noise and DWI Sampling. *Magn Reson Med* (2017) **78**:1767–1780.  
478 doi:10.1002/mrm.26575
- 479 29. Fortin J-P, Parker D, Tunç B, Watanabe T, Elliott MA, Ruparel K, Roalf DR,  
480 Satterthwaite TD, Gur RC, Gur RE, et al. Harmonization of multi-site diffusion tensor imaging  
481 data. *NeuroImage* (2017) **161**:149–170. doi:10.1016/j.neuroimage.2017.08.047
- 482 30. Pohl KM, Sullivan EV, Rohlfing T, Chu W, Kwon D, Nichols BN, Zhang Y, Brown SA,  
483 Tapert SF, Cummins K, et al. Harmonizing DTI measurements across scanners to examine  
484 the development of white matter microstructure in 803 adolescents of the NCANDA study.  
485 *NeuroImage* (2016) **130**:194–213. doi:10.1016/j.neuroimage.2016.01.061
- 486 31. Grech-Sollars M, Hales PW, Miyazaki K, Raschke F, Rodriguez D, Wilson M, Gill SK,  
487 Banks T, Saunders DE, Clayden JD, et al. Multi-centre reproducibility of diffusion MRI  
488 parameters for clinical sequences in the brain: Multi-centre reproducibility of diffusion MRI  
489 using clinical sequences. *NMR Biomed* (2015) **28**:468–485. doi:10.1002/nbm.3269
- 490 32. Prohl AK, Scherrer B, Tomas-Fernandez X, Filip-Dhima R, Kapur K, Velasco-Annis C,  
491 Clancy S, Carmody E, Dean M, Valle M, et al. Reproducibility of Structural and Diffusion  
492 Tensor Imaging in the TACERN Multi-Center Study. *Front Integr Neurosci* (2019) **13**:24.

493 doi:10.3389/fnint.2019.00024

494 33. Jockwitz C, Mérillat S, Liem F, Oschwald J, Amunts K, Caspers S, Jäncke L.  
495 Generalizing age effects on brain structure and cognition: A two-study comparison approach.  
496 *Hum Brain Mapp* (2019) **40**:2305–2319. doi:10.1002/hbm.24524

497 34. Jahanshad N, Kochunov PV, Sprooten E, Mandl RC, Nichols TE, Almasy L, Blangero  
498 J, Brouwer RM, Curran JE, de Zubicaray GI, et al. Multi-site genetic analysis of diffusion  
499 images and voxelwise heritability analysis: A pilot project of the ENIGMA–DTI working group.  
500 *NeuroImage* (2013) **81**:455–469. doi:10.1016/j.neuroimage.2013.04.061

501 35. Kochunov P, Jahanshad N, Sprooten E, Nichols TE, Mandl RC, Almasy L, Booth T,  
502 Brouwer RM, Curran JE, de Zubicaray GI, et al. Multi-site study of additive genetic effects on  
503 fractional anisotropy of cerebral white matter: Comparing meta and megaanalytical  
504 approaches for data pooling. *NeuroImage* (2014) **95**:136–150.  
505 doi:10.1016/j.neuroimage.2014.03.033

506 36. Chad JA, Pasternak O, Salat DH, Chen JJ. Re-examining age-related differences in  
507 white matter microstructure with free-water corrected diffusion tensor imaging. *Neurobiol*  
508 *Aging* (2018) **71**:161–170. doi:10.1016/j.neurobiolaging.2018.07.018

509 37. Wu Y-C, Field AS, Whalen PJ, Alexander AL. Age- and gender-related changes in the  
510 normal human brain using hybrid diffusion imaging (HYDI). *NeuroImage* (2011) **54**:1840–  
511 1853. doi:10.1016/j.neuroimage.2010.09.067

512 38. Sullivan EV, Adalsteinsson E, Hedehus M, Ju C, Moseley M, Lim KO, Pfefferbaum A.  
513 Equivalent disruption of regional white matter microstructure in ageing healthy men and  
514 women: *Neuroreport* (2001) **12**:99–104. doi:10.1097/00001756-200101220-00027

515 39. Hasan KM, Kamali A, Abid H, Kramer LA, Fletcher JM, Ewing-Cobbs L. Quantification  
516 of the spatiotemporal microstructural organization of the human brain association, projection  
517 and commissural pathways across the lifespan using diffusion tensor tractography. *Brain*  
518 *Struct Funct* (2010) **214**:361–373. doi:10.1007/s00429-009-0238-0

519 40. Kochunov P, Glahn DC, Lancaster J, Thompson PM, Kochunov V, Rogers B, Fox P,  
520 Blangero J, Williamson DE. Fractional anisotropy of cerebral white matter and thickness of

- 521 cortical gray matter across the lifespan. *NeuroImage* (2011) **58**:41–49.  
522 doi:10.1016/j.neuroimage.2011.05.050
- 523 41. Hsu J-L, Leemans A, Bai C-H, Lee C-H, Tsai Y-F, Chiu H-C, Chen W-H. Gender  
524 differences and age-related white matter changes of the human brain: A diffusion tensor  
525 imaging study. *NeuroImage* (2008) **39**:566–577. doi:10.1016/j.neuroimage.2007.09.017
- 526 42. Fjell AndersM, Walhovd KB, Westlye LT, Østby Y, Tamnes CK, Jernigan TL, Gamst  
527 A, Dale AM. When does brain aging accelerate? Dangers of quadratic fits in cross-sectional  
528 studies. *NeuroImage* (2010) **50**:1376–1383. doi:10.1016/j.neuroimage.2010.01.061
- 529 43. Pfefferbaum A, Sullivan EV. Cross-sectional versus longitudinal estimates of age-  
530 related changes in the adult brain: overlaps and discrepancies. *Neurobiol Aging* (2015)  
531 **36**:2563–2567. doi:10.1016/j.neurobiolaging.2015.05.005
- 532 44. Lebel C, Walker L, Leemans A, Phillips L, Beaulieu C. Microstructural maturation of  
533 the human brain from childhood to adulthood. *NeuroImage* (2008) **40**:1044–1055.  
534 doi:10.1016/j.neuroimage.2007.12.053
- 535 45. Lebel C, Beaulieu C. Longitudinal Development of Human Brain Wiring Continues from  
536 Childhood into Adulthood. *J Neurosci* (2011) **31**:10937–10947.  
537 doi:10.1523/JNEUROSCI.5302-10.2011
- 538 46. Kodiweera C, Alexander AL, Harezlak J, McAllister TW, Wu Y-C. Age effects and sex  
539 differences in human brain white matter of young to middle-aged adults: A DTI, NODDI, and  
540 q-space study. *NeuroImage* (2016) **128**:180–192. doi:10.1016/j.neuroimage.2015.12.033
- 541 47. Tian L, Ma L. Microstructural Changes of the Human Brain from Early to Mid-  
542 Adulthood. *Front Hum Neurosci* (2017) **11**:393. doi:10.3389/fnhum.2017.00393
- 543

544 **8 Tables**

545 **Table 1.** Basic statistics for the 10 contributing datasets. MRi-Share: Magnetic Resonance imaging subcohort of Internet-based Students HeAlth Research Enterprise;  
 546 BIL&GIN: Brain Imaging of Lateralization study at Groupe d’Imagerie Neurofonctionnelle; SYS cohort: Saguenay Youth Study; ASPSF: Austrian Stroke Prevention  
 547 Study Family; OATS: Older Australian Twin Study; LBC 1936: Lothian Birth Cohort; MAS: Memory and Ageing Study. TIV: total intracranial volume estimated with  
 548 Freesurfer 5.3 version except “\*\*” with FreeSurfer 6.0 version. † data subsample size < 30 (not included in the age category statistical analysis)

Dataset		MRi-Share	BIL&GIN	SYS	LIFE	1000 BRAINS	UKBiobank	ASPSF	OATS	LBC 1936	MAS
<b>Sample size</b>	<b>20,005</b>	1,824	410	512	1,906	1,209	12,397	277	386	672	412
	(% females)	72%	51%	54%	51%	44%	53%	60%	64%	47%	53%
<b>Age (years)</b>	mean (SD)	22.1 (2.3)	26.9 (8.0)	49.5 (5.0)	58.1 (15.1)	60.8 (13.4)	62.6 (7.4)	65.0 (11.1)	71.1 (5.1)	72.7 (0.7)	80.3 (4.6)
	range	[18.1, 34.9]	[18.1, 57.2]	[36.4, 65.4]	[19.0, 82.0]	[18.5, 85.4]	[45.1, 80.3]	[38.5, 85.6]	[65.4, 89.5]	[71.0, 74.2]	[72.7, 92.6]
<b>TIV (cm<sup>3</sup>)</b>	females	1515 (104)*	1323 (93)	1348 (164)	1637 (115)	1401 (104)	1466 (203)*	1396 (110)	1369 (133)	1353 (100)	1267 (141)
	mean (SD) males	1703 (118)*	1503 (127)	1622 (131)	1831 (131)	1570 (118)	1576 (147)*	1572 (118)	1574 (138)	1537 (112)	1460 (163)
<b>N per age category</b>	<b>18 to 28</b> (2,200)	1,778	285	0	101	36	0	0	0	0	0
	<b>28 to 38</b> (340)	46	84	3 <sup>†</sup>	142	65	0	0	0	0	0
	<b>38 to 48</b> (707)	0	24 <sup>†</sup>	176	250	93	126 <sup>††</sup>	38	0	0	0
	<b>48 to 58</b> (4,287)	0	17 <sup>†</sup>	311	218	176	3,525	40	0	0	0
	<b>58 to 68</b> (6,535)	0	3 <sup>†</sup>	22 <sup>†</sup>	511	431	5,375	52 <sup>††</sup>	144 <sup>††</sup>	0	0
	<b>68 to 78</b> (5,515)	0	0	0	656	358	3,351	129	195	672	154
	<b>78 to 98</b> (421)	0	0	0	28 <sup>†</sup>	50	20 <sup>†</sup>	18 <sup>†</sup>	47	0	258

549

550

551  
552

**Table 2.** Diffusion-weighted imaging acquisition the 10 contributing datasets. (see Table1 legend for the meaning of dataset abbreviated names and supplementary material section for a more detailed description of these datasets). \*: multi-shell acquisition.

Dataset	MRI-Share	BIL&GIN	SYS	LIFE	1000 BRAINS	UKBiobank	ASPSF	OATS	LBC 1936	MAS
<b>MRI scanner</b>	SIEMENS PRISMA	PHILIPS ACHIEVA	SIEMENS	SIEMENS VERIO	SIEMENS TIM TRIO	SIEMENS SKYRA	SIEMENS TIM TRIO	PHILIPS (x2) SIEMENS(x2)	GE Signa Horizon HDxt	PHILIPS ACHIEVA Quasar Dual
<b>B0 strength</b>	3T	3T	1.5T	3T	3T	3T	3T	1.5T & 3T	1.5T	3T
<b>b-gradient (s/mm<sup>2</sup>)</b>	1000*	1000	1000	1000	1000	1000*	1000	1000	1000	700 or 1000
<b>Nr of directions</b>	32	2 x 21	64	60	30	50	6 or 12	32	64	6 or 32
<b>Voxel size (mm<sup>3</sup>)</b>	1.7x1.7x1.8	2x2x2	2.3x2.3x3	1.7x1.7x1.7	2x2x2	2x2x2	1.8x1.8x2.5	2.5x2.5x2.5	2x2x2	2.5x2.5x2.5
<b>TR (ms)</b>	3540 (multiband x3)	8500	8000	13,800	7800	3600 (multiband x3)	4900 or 6700	7800 or 8600	16500	7800
<b>TE (ms)</b>	75	81	102	100	83	92	81 or 95	68 or 96	98	68
<b>Acquisition duration</b>	9'45	7'45	10'	16'08	4'30	9'45	4'51 or 6'10	4'40 or 4'56	19'30	4'40

553  
554

555 **Table 3a.** Basic statistics of axial diffusivity (AD, in  $\text{mm}^2\text{sec}^{-1} \times 10^{-4}$ ) average across a white matter skeleton for each age category and each contributing dataset.  
 556 Values are mean (S.D. and range [min, max] across the age category sample). See Table1 legend for the meaning of dataset abbreviated names

Age range	MRi-Share	BIL&GIN	SYS	LIFE	1000 BRAINS	UKBiobank	ASPSF	OATS	LBC 1936	MAS
<b>18 to 28</b>	11.80 (0.19) [10.87, 12.45]	12.70 (0.18) [12.26, 13.18]		12.39 (0.23) [11.70, 13.10]	11.60 (0.20) [11.09, 11.96]					
<b>28 to 38</b>	11.68 (0.21) [11.10, 12.12]	12.58 (0.17) [12.14, 13.04]		12.33 (0.20) [11.80, 12.90]	11.41 (0.27) [10.71, 11.95]					
<b>38 to 48</b>		12.45 (0.21) [12.07, 12.88]	11.58 (0.22) [11.03, 12.29]	12.25 (0.21) [11.60, 12.80]	11.33 (0.25) [10.52, 11.89]	12.21 (0.27) [10.76, 12.85]	11.88 (0.24) [11.50, 12.46]			
<b>48 to 58</b>			11.58 (0.23) [11.01, 12.38]	12.25 (0.24) [11.40, 13.10]	11.31 (0.25) [10.59, 12.02]	12.21 (0.25) [10.18, 13.03]	11.89 (0.27) [11.42, 12.68]			
<b>58 to 68</b>			11.67 (0.24) [11.24, 12.21]	12.34 (0.26) [11.60, 13.20]	11.37 (0.30) [10.30, 12.32]	12.25 (0.26) [10.52, 13.24]	12.03 (0.30) [11.41, 12.76]	11.74 (0.49) [10.61, 12.80]		
<b>68 to 78</b>				12.48 (0.28) [11.40, 13.40]	11.50 (0.32) [10.36, 12.58]	12.34 (0.29) [10.70, 13.53]	12.06 (0.37) [9.69, 12.88]	11.83 (0.58) [10.69, 13.18]	9.79 (0.43) [8.41, 10.94]	11.83 (0.31) [11.06, 12.56]
<b>78 to 98</b>				12.49 (0.30) [11.90, 13.20]	11.64 (0.33) [11.07, 12.47]	12.44 (0.27) [11.66, 12.83]		12.12 (0.62) [10.80, 13.49]		11.96 (0.32) [10.99, 13.05]

557

558

559 **Table 3b.** Basic statistics of radial diffusivity (RD, in  $\text{mm}^2\text{sec}^{-1} \times 10^{-4}$ ) average across a white matter skeleton for each age category and each contributing dataset.  
 560 Values are mean (S.D. and range [min, max] across the age category sample. (see Table1 legend for the meaning of dataset abbreviated names)

Age range	MRi-Share	BIL&GIN	SYS	LIFE	1000 BRAINS	UKBiobank	ASPSF	OATS	LBC 1936	MAS
18 to 28	4.74 (0.18) [4.15, 5.53]	4.81 (0.19) [4.26, 5.44]		4.83 (0.19) [4.33, 5.29]	4.66 (0.18) [4.26, 5.19]					
28 to 38	4.72 (0.21) [4.35, 5.10]	4.79 (0.20) [4.45, 5.56]		4.83 (0.20) [4.42, 5.36]	4.60 (0.18) [4.20, 5.17]					
38 to 48		4.83 (0.22) [4.49, 5.27]	5.45 (0.24) [4.88, 6.36]	4.87 (0.22) [4.35, 5.59]	4.64 (0.20) [4.28, 5.27]	4.95 (0.22) [4.19, 5.64]	5.11 (0.29) [4.54, 5.79]			
48 to 58			5.51 (0.25) [4.93, 6.54]	4.99 (0.24) [4.47, 6.01]	4.72 (0.22) [4.21, 5.38]	4.97 (0.23) [4.17, 6.22]	5.22 (0.30) [4.57, 6.05]			
58 to 68			5.58 (0.31) [5.02, 6.27]	5.13 (0.29) [4.29, 6.36]	4.84 (0.25) [4.21, 5.57]	5.08 (0.26) [4.34, 6.40]	5.47 (0.37) [4.73, 6.59]	5.27 (0.38) [4.36, 6.05]		
68 to 78				5.31 (0.33) [4.48, 6.73]	4.99 (0.31) [4.16, 6.29]	5.21 (0.29) [4.29, 7.10]	5.49 (0.35) [4.85, 6.69]	5.40 (0.46) [4.44, 6.77]	5.21 (0.38) [4.28, 8.87]	5.66 (0.34) [5.05, 6.78]
78 to 98				5.37 (0.33) [4.87, 6.31]	5.19 (0.37) [4.69, 5.99]	5.36 (0.20) [5.03, 5.69]		5.75 (0.48) [4.80, 7.08]		5.81 (0.40) [4.88, 7.17]

561

562



563 **Table 3c.** Basic statistics of mean diffusivity (MD, in  $\text{mm}^2\text{sec}^{-1} \times 10^{-4}$ ) average across a white matter skeleton for each age category and each contributing dataset.  
 564 Values are mean (S.D. and range [min, max] across the age category sample. (see Table1 legend for the meaning of dataset abbreviated names)

Age range	MRI-Share	BIL&GIN	SYS	LIFE	1000 BRAINS	UKBiobank	ASPSF	OATS	LBC 1936	MAS
18 to 28	7.09 (0.16) [6.54, 7.76]	7.44 (0.17) [7.02, 7.98]		7.35 (0.18) [6.89, 7.75]	6.97 (0.17) [6.54, 7.34]					
28 to 38	7.04 (0.18) [6.64, 7.38]	7.39 (0.17) [7.08, 7.97]		7.33 (0.18) [6.92, 7.78]	6.87 (0.19) [6.43, 7.39]					
38 to 48		7.37 (0.20) [7.05, 7.80]	7.50 (0.21) [6.98, 8.17]	7.33 (0.20) [6.81, 7.84]	6.87 (0.19) [6.42, 7.39]	7.37 (0.22) [6.38, 8.05]	7.37 (0.25) [6.97, 8.01]			
48 to 58			7.53 (0.23) [6.97, 8.45]	7.41 (0.22) [6.89, 8.31]	6.92 (0.21) [6.35, 7.58]	7.39 (0.22) [6.17, 8.42]	7.45 (0.27) [6.91, 8.26]			
58 to 68			7.61 (0.27) [7.09, 8.20]	7.53 (0.26) [6.82, 8.64]	7.01 (0.25) [6.35, 7.78]	7.47 (0.24) [6.41, 8.67]	7.66 (0.34) [6.98, 8.58]	7.43 (0.41) [6.55, 8.18]		
68 to 78				7.70 (0.30) [6.93, 8.92]	7.16 (0.29) [6.30, 8.39]	7.59 (0.27) [6.43, 9.23]	7.68 (0.33) [6.51, 8.74]	7.54 (0.48) [6.57, 8.91]	6.74 (0.35) [5.79, 7.86]	7.72 (0.31) [7.14, 8.71]
78 to 98				7.74 (0.31) [7.23, 8.61]	7.34 (0.34) [6.84, 8.15]	7.72 (0.20) [7.34, 8.01]		7.87 (0.51) [6.92, 9.21]		7.86 (0.36) [6.96, 9.06]

565

566

567  
568

**Table 3d.** Basic statistics of peak width skeletonized mean diffusivity (PSMD, in  $\text{mm}^2\text{sec}^{-1} \times 10^{-4}$ ) for each age category and each contributing dataset. Values are mean (S.D. and range [min, max] across the age category sample. (see Table1 legend for the meaning of dataset abbreviated names.

Age range	MRi-Share	BIL&GIN	SYS	LIFE	1000 BRAINS	UKBiobank	ASPSF	OATS	LBC 1936	MAS
18 to 28	1.54 (0.14) [1.20, 2.13]	2.13 (0.17) [1.75, 2.78]		2.02 (0.19) [1.68, 2.53]	2.26 (0.28) [1.86, 3.47]					
28 to 38	1.58 (0.17) [1.33, 2.01]	2.18 (0.22) [1.75, 2.85]		2.05 (0.19) [1.65, 2.63]	2.32 (0.24) [1.75, 3.00]					
38 to 48		2.24 (0.18) [1.89, 2.58]	2.68 (0.30) [2.07, 4.44]	2.17 (0.22) [1.64, 3.00]	2.49 (0.29) [1.94, 3.46]	2.10 (0.22) [1.60, 3.11]	2.63 (0.39) [1.95, 3.53]			
48 to 58			2.82 (0.34) [1.99, 5.12]	2.31 (0.28) [1.70, 3.63]	2.67 (0.32) [2.03, 4.07]	2.12 (0.25) [1.49, 4.58]	2.69 (0.36) [2.18, 3.70]			
58 to 68			2.92 (0.30) [2.51, 3.57]	2.53 (0.38) [1.83, 4.85]	2.94 (0.38) [2.14, 5.03]	2.27 (0.31) [1.56, 5.71]	2.82 (0.49) [2.15, 4.54]	2.96 (0.54) [2.11, 4.90]		
68 to 78				2.78 (0.47) [1.88, 5.26]	3.26 (0.47) [2.23, 5.53]	2.48 (0.39) [1.61, 6.19]	3.17 (0.49) [2.15, 4.60]	3.10 (0.64) [2.17, 6.66]	3.18 (0.53) [2.09, 5.72]	3.84 (0.61) [2.56, 6.02]
78 to 98				2.96 (0.45) [2.15, 3.94]	3.68 (0.58) [2.83, 5.32]	2.74 (0.33) [2.10, 3.45]		3.77 (0.90) [2.47, 6.51]		4.29 (0.77) [2.95, 7.96]

569  
570

571 **Table 3e.** Basic statistics of fractional anisotropy (FA, unitless) average across individual FA skeleton for each age range category and each contributing dataset.  
 572 Values are mean (S.D. and range [min, max]) across the age category sample. (see Table1 legend for the meaning of dataset abbreviated names)

Age range	MRi-Share	BIL&GIN	SYS	LIFE	1000 BRAINS	UKBiobank	ASPSF	OATS	LBC 1936	MAS
18 to 28	0.53 (0.01) [0.47, 0.58]	0.56 (0.01) [0.51, 0.60]		0.54 (0.02) [0.49, 0.58]	0.54 (0.01) [0.49, 0.56]					
28 to 38	0.53 (0.02) [0.49, 0.56]	0.55 (0.02) [0.50, 0.58]		0.54 (0.02) [0.50, 0.58]	0.54 (0.01) [0.49, 0.57]					
38 to 48		0.55 (0.02) [0.52, 0.57]	0.46 (0.02) [0.39, 0.50]	0.54 (0.02) [0.48, 0.58]	0.53 (0.02) [0.48, 0.56]	0.53 (0.01) [0.49, 0.56]	0.51 (0.02) [0.46, 0.55]			
48 to 58			0.45 (0.02) [0.40, 0.50]	0.53 (0.02) [0.46, 0.57]	0.52 (0.02) [0.47, 0.58]	0.52 (0.02) [0.44, 0.57]	0.49 (0.02) [0.42, 0.54]			
58 to 68			0.45 (0.02) [0.41, 0.49]	0.52 (0.02) [0.44, 0.58]	0.51 (0.02) [0.46, 0.57]	0.52 (0.02) [0.44, 0.57]	0.48 (0.02) [0.41, 0.53]	0.48 (0.02) [0.43, 0.55]		
68 to 78				0.51 (0.02) [0.40, 0.56]	0.51 (0.02) [0.44, 0.56]	0.51 (0.02) [0.37, 0.57]	0.48 (0.02) [0.41, 0.53]	0.48 (0.03) [0.38, 0.54]	0.41 (0.03) [0.31, 0.47]	0.45 (0.02) [0.36, 0.49]
78 to 98				0.50 (0.02) [0.45, 0.54]	0.50 (0.02) [0.44, 0.53]	0.50 (0.01) [0.48, 0.52]		0.46 (0.02) [0.40, 0.51]		0.45 (0.03) [0.34, 0.51]

573

574

575

576  
577

**Table 4.** ANOVA effect of age (estimate (standard error) and significance p-value) on five DTI metrics (AD, RD, MD, PSMD, and FA evaluated across individual FA skeletons). Values are in  $\text{mm}^2\text{s}^{-1}\text{year}^{-1} \times 10^{-6}$  for AD, RD and MD, in  $\text{mm}^2\text{s}^{-1}\text{year}^{-1} \times 10^{-7}$  for PSMD, and in  $\text{year}^{-1} \times 10^{-3}$  for FA.

Age range (years)	AD		RD		MD		PSMD		FA	
	estimate	p	estimate	p	estimate	p	estimate	p	estimate	p
18 to 28	-2.01 (0.20)	< 0.0001	-1.06 (0.18)	< 0.0001	-1.38 (0.17)	< 0.0001	0.41 (0.15)	0.0058	0.30 (0.15)	0.041
28 to 38	-1.32 (0.43)	0.0023	-0.22 (0.41)	0.59	-0.58 (0.37)	0.12	0.60 (0.42)	0.15	-0.27 (0.32)	0.40
38 to 48	-0.68 (0.37)	0.065	0.40 (0.37)	0.27	0.047 (0.33)	0.89	1.84 (0.41)	< 0.0001	-0.54 (0.27)	0.046
48 to 58	-0.11 (0.13)	0.41	0.61 (0.12)	< 0.0001	0.37 (0.12)	0.0019	1.11 (0.14)	< 0.0001	-0.56 (0.09)	< 0.0001
58 to 68	0.95 (0.12)	< 0.0001	1.46 (0.11)	< 0.0001	1.29 (0.11)	< 0.0001	2.18 (0.14)	< 0.0001	-0.91 (0.08)	< 0.0001
68 to 78	1.75 (0.19)	< 0.0001	1.94 (0.18)	< 0.0001	1.87 (0.17)	< 0.0001	3.67 (0.24)	< 0.0001	-0.97 (0.12)	< 0.0001
78 to 98	2.30 (0.60)	0.0002	4.01 (0.64)	< 0.0001	3.44 (0.59)	< 0.0001	6.99 (0.12)	< 0.0001	-2.36 (0.39)	< 0.0001

578  
579

580 **Table 5.** ANOVA effect of sex and TIV (estimate (standard error) and significance p-value) on five DTI metrics (AD, RD, MD, PSMD, and FA evaluated across  
 581 individual FA skeletons). TIV: total intracranial volume. Values for the effects of sex are in  $\text{mm}^2\text{s}^{-1} \times 10^{-6}$  for AD, RD, MD, and PSMD and in  $\times 10^{-3}$  for FA, and for the  
 582 effects of TIV are in  $\text{mm}^2\text{s}^{-1}\text{cm}^{-3} \times 10^{-6}$  for AD, RD MD, and PSMD and in  $\text{cm}^{-3} \times 10^{-5}$  for FA.

Effect	AD		RD		MD		PSMD		FA	
	estimate	p	estimate	p	estimate	p	estimate	p	estimate	p
<b>Sex (F-M)</b>	1.13 (0.21)	< 0.0001	0.45 (0.21)	0.032	0.68 (0.19)	0.0005	-5.34 (0.26)	< 0.0001	0.04 (0.14)	0.74
<b>TIV</b>	1.41 (0.12)	< 0.0001	0.07 (0.12)	0.53	0.52 (0.01)	< 0.0001	1.43 (0.15)	< 0.0001	0.54 (0.08)	< 0.0001

583

584

585 **9 Figure legends**

586 **Figure 1.** Box-plots and histogram distribution of the age of the participants of the 10  
587 contributing datasets.

588 **Figure 2.** Mean and standard deviation (bars) of the five DTI metrics for each age  
589 subcategory and each dataset. The dotted lines connect values for the different age  
590 categories of the same dataset.

591 **Figure 3.** Coefficients of variation of the five DTI metrics for each age subcategory and each  
592 dataset.

593 **Figure 4.** ANOVA estimates and 95% confidence intervals of the effects of age on the five  
594 DT metrics for each age subcategory. Units are  $\text{mm}^2/\text{s}/\text{year} \times 10^{-3}$  for AD, RD and MD,  
595  $\text{mm}^2/\text{s}/\text{year} \times 10^{-4}$  for PSMD,  $1/\text{year} \times 10^{-3}$  for FA.

596 **Figure 5.** ANOVA estimates and 95% confidence intervals of the effects of age on the five  
597 DT metrics for each age subcategory and each dataset.

598

599 **10 Conflict of Interest**

600 The authors declare that the research was conducted in the absence of any commercial or  
601 financial relationships that could be construed as a potential conflict of interest.

602 **11 Data Availability Statement**

603 Requests to access these datasets should be directed to:

MRi-Share	B Mazoyer	bernard.mazoyer@u-bordeaux.fr
BIL&GIN	B Mazoyer	bernard.mazoyer@u-bordeaux.fr
LIFE	A Villringer	villringer@cbs.mpg.de
SYS	T Paus	tpaus@research.baycrest.org
1000BRAINS	S Caspers	s.caspers@fz-juelich.de
UKBIOBANK		www.ukbiobank.ac.uk
ASPSF	R Schmidt	reinhold.schmidt@medunigraz.at
OATS	P Sachdev	p.sachdev@unsw.edu.au
LBC1936	I Deary	i.deary@ed.ac.uk
MAS	P Sachdev	p.sachdev@unsw.edu.au

604











