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► 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

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

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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 95th and 5th 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 7.6×10^{-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: 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).

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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
Sample size	20,005	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%
Age (years)	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]
TIV (cm³)	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)
N per age category	18 to 28 (2,200)	1,778	285	0	101	36	0	0	0	0	0
	28 to 38 (340)	46	84	3 [†]	142	65	0	0	0	0	0
	38 to 48 (707)	0	24 [†]	176	250	93	126 ^{††}	38	0	0	0
	48 to 58 (4,287)	0	17 [†]	311	218	176	3,525	40	0	0	0
	58 to 68 (6,535)	0	3 [†]	22 [†]	511	431	5,375	52 ^{††}	144 ^{††}	0	0
	68 to 78 (5,515)	0	0	0	656	358	3,351	129	195	672	154
	78 to 98 (421)	0	0	0	28 [†]	50	20 [†]	18 [†]	47	0	258

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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
MRI scanner	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
B0 strength	3T	3T	1.5T	3T	3T	3T	3T	1.5T & 3T	1.5T	3T
b-gradient (s/mm²)	1000*	1000	1000	1000	1000	1000*	1000	1000	1000	700 or 1000
Nr of directions	32	2 x 21	64	60	30	50	6 or 12	32	64	6 or 32
Voxel size (mm³)	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
TR (ms)	3540 (multiband x3)	8500	8000	13,800	7800	3600 (multiband x3)	4900 or 6700	7800 or 8600	16500	7800
TE (ms)	75	81	102	100	83	92	81 or 95	68 or 96	98	68
Acquisition duration	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

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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
18 to 28	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]					
28 to 38	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]					
38 to 48		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]			
48 to 58			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]			
58 to 68			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]		
68 to 78				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]
78 to 98				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]

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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]

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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]

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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]

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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]

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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

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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
Sex (F-M)	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
TIV	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

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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.

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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:

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