

1 **Childhood socio-economic disadvantage predicts reduced myelin growth**  
2 **across adolescence and young adulthood**

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34 **Classification**

35 Major: Biological Sciences

36 Minor: Neuroscience

## 37 **Abstract**

38 Socio-economic disadvantage (SED) increases exposure to life stressors. Animal research suggests  
39 early life stressors affect later neurodevelopment, including myelin developmental growth. To  
40 determine whether human childhood SED affects myelination in adolescence and early adulthood we  
41 measured the developmental increase of a sensitive myelin marker, magnetization transfer (MT), in a  
42 longitudinal study. Childhood SED was associated with globally reduced MT, as well as slower intra-  
43 cortical MT increase in widespread sensory-motor, cingulate, insular and prefrontal areas and  
44 subcortical areas. Parental education partially accounted for the SED effects on MT increase, while  
45 positive parenting provided a partial protection against the impact of SED. Thus, early socio-economic  
46 disadvantage, a vulnerability factor for a range of ill-health outcomes, is a risk factor for aberrant  
47 myelin growth during a critical developmental period that is associated with a high risk of psychiatric  
48 disorder.

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## 50 **Keywords**

51 Myelin, magnetization transfer, development, quantitative imaging, socio-economic disadvantage,  
52 adolescence, young adulthood, parenting, parental education, longitudinal

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## 55 Introduction

56 Socio-economic disadvantage (SED) increases exposure to childhood adversity (Pascoe et al., 2016).  
57 In turn, adversity is associated with specific patterns of impairments in human brain development  
58 (Evans & Cassells, 2014; Johnson, Riis, & Noble, 2016; McDermott et al., 2019; Whittle et al., 2017).  
59 The impact of early life socio-economic disadvantage (SED) on brain development is poorly  
60 understood at the microstructural level. Here, we make use of a unique longitudinal sample of young  
61 people and *in-vivo* quantitative MRI, a measure of macromolecular content sensitive to myelin  
62 content, to examine the effects of SED on myelin development.

63 Animal studies, where early stressors are under experimental control, show a causal impact of  
64 adversity on brain growth, even during adolescent development (Howell et al., 2013; Liu et al., 2012;  
65 Zhang, 2017). Some experimental manipulations, such as variable foraging demand (Coplan et al.,  
66 2016, 2006), bear resemblance to the resource uncertainty encountered in human SED, but it is still  
67 difficult to generalize from animal stress to human disadvantage. Thus, mindful of the dangers of  
68 making causal implications (Wax, 2017), it is important to map longitudinally human microstructural  
69 brain changes such as myelination in relation to SED. This can allow a more detailed comparison with  
70 animal findings, and close a causal explanatory gap (Donahue et al., 2018). Cortical myelin likely  
71 reflects local neuritic insulation and fibre density (Glasser et al., 2014). It enables myeloarchitectonic  
72 parcellation (Glasser et al. 2016) and influences neuronal dynamics (Demirtas et al., 2019).

73 We recently mapped neurotypical myelin development during adolescence and young adulthood,  
74 using myelin-sensitive magnetization transfer saturation (MT) (see also Turati et al., 2015) and  
75 showed myelin growth is tied to mental health traits (Ziegler et al., 2018). Human neuroimaging  
76 studies, for example in childhood as a function of cortisol reactivity (Sheikh et al., 2014) or in young  
77 adulthood as a function of developmental stressors (Jensen et al., 2017), have linked adversity to  
78 alterations in white matter myelin. However, these findings beg the question as to how myelination  
79 unfolds in detail during adolescence, in both cortex and adjacent white matter, as a function of early  
80 socio-economic disadvantage, rather than of specific stressors.

81 Here we seek to clarify whether patterns of longitudinal myelin growth during late development are  
82 associated with early SED as well as establish what role parenting plays in mediating or moderating  
83 any relationship (Hair, Hanson, Wolfe, & Pollak, 2015; Noble et al., 2015; Whittle et al., 2017). Under  
84 the hypothesis that SED impacts brain development, we predicted that neighbourhood-level indices  
85 of deprivation would be associated with both the mean level of myelination, and rate of myelin  
86 growth, during late brain development. We found evidence in support of the latter but not the  
87 former. Family factors, specifically lower parental education and poorer reported parenting,  
88 explained important aspects of the observed relationship.

## 89 Results

### 90 Early disadvantage is associated with slower myelin growth

91 We obtained 497 repeated structural MRI scans on 288 (51.7% female) healthy participants between  
92 14 and 25 years of age (see Methods). We used an observational accelerated-longitudinal design of  
93 these community dwelling English young people and focused on longitudinal findings, a focus which  
94 obviated biases seen in cross-sectional estimates with respect to development (Lindenberger, Von  
95 Oertzen, Ghisletta, & Hertzog, 2011). We used MT rather than morphometric indices as a measure of

96 (myelin) development, following the priorities highlighted recently by neurodevelopmental  
97 researchers (Walhovd, Fjell, Giedd, Dale, & Brown, 2017).

98 We analysed grey and white matter MT growth related to age, within as well as across participants,  
99 using the efficient 'sandwich estimator' (Guillaume et al., 2014) and adjusting for curvilinear  
100 trajectories (for details cf. methods and Ziegler et al., 2018 focussing on effects of demographics on  
101 MT in same sample). This analysis allowed us to index selected longitudinal results in terms of MT  
102 growth rate (over follow-up visits) adjusting for the participants' baseline age.

103 Our primary measure of SED was the neighbourhood poverty index (NPI), provided by the UK Office  
104 of National Statistics (Fry, 2010). NPI was available for all 288 participants at the time of scanning,  
105 and for 185 (45.7% female) of these participants before 12 years of age (Supplementary Figure S1).  
106 We examined putative explanatory variables both by entering them as covariates and moderating  
107 factors in the imaging analyses (cf. methods).

108 Strikingly, we found that worse early life SED (i.e. living in a more deprived neighbourhood in before  
109 age 12) correlated robustly with reduced rate of MT increase (MTr) in multiple brain areas (Figure 1  
110 and Supplementary table 1). This supported an hypothesis that SED is associated with reduced  
111 myelin growth (accounting for age and visits) during late adolescent development (Howell et al.,  
112 2013; Jensen et al., 2017). Moreover, a reduction in MTr was also observed globally (MTr within  
113 whole-brain grey matter,  $t(321)=-2.87$ ,  $p=.0022$ , one-sided, cf. methods). This contrasted with  
114 current abode in a disadvantaged neighbourhood, which predicted reduced growth only weakly  
115 (Supplementary Figure S2). Furthermore, there were no brain areas where SED was significantly  
116 associated with increased MTr (or MTm), which might be expected if some changes reflected  
117 adaptive or compensatory early growth (Ono et al., 2008; Ziegler et al., 2018).

118 Early life SED correlated with reduced intra-cortical MTr across multiple brain regions including mid-  
119 and posterior cingulate, precuneus, operculum, insula (Figure 1a-b) and prefrontal areas, especially  
120 on the right. Interestingly, MTr of juxta-cortical white matter and also subcortical regions was  
121 similarly reduced (Figure 1b-c, Supplementary table 2). These rate reductions were most  
122 pronounced in highly myelinated areas (e.g. M1, S1; for maps see e.g. Glasser et al., 2014) and in  
123 regions showing significant developmental MT increase in the very same group of participants  
124 (Ziegler et al., 2018).

125 Our hypothesis that the mean level of myelin, as reflected by the mean MT over visits would show a  
126 similar reduction with SED was supported at the global brain level (MTm; accounting for age, visit,  
127 sex, and confounds - see methods). Higher SED was associated with reduced global MTm ( $t=-2.15$ ,  
128  $p=.016$ , one-sided,  $df=321$ ). The local analysis however showed no significant associations between  
129 early life SED and MTm (FDR corrected). In the light of the significant global result, greater statistical  
130 power may be needed to resolve local MTm effects.

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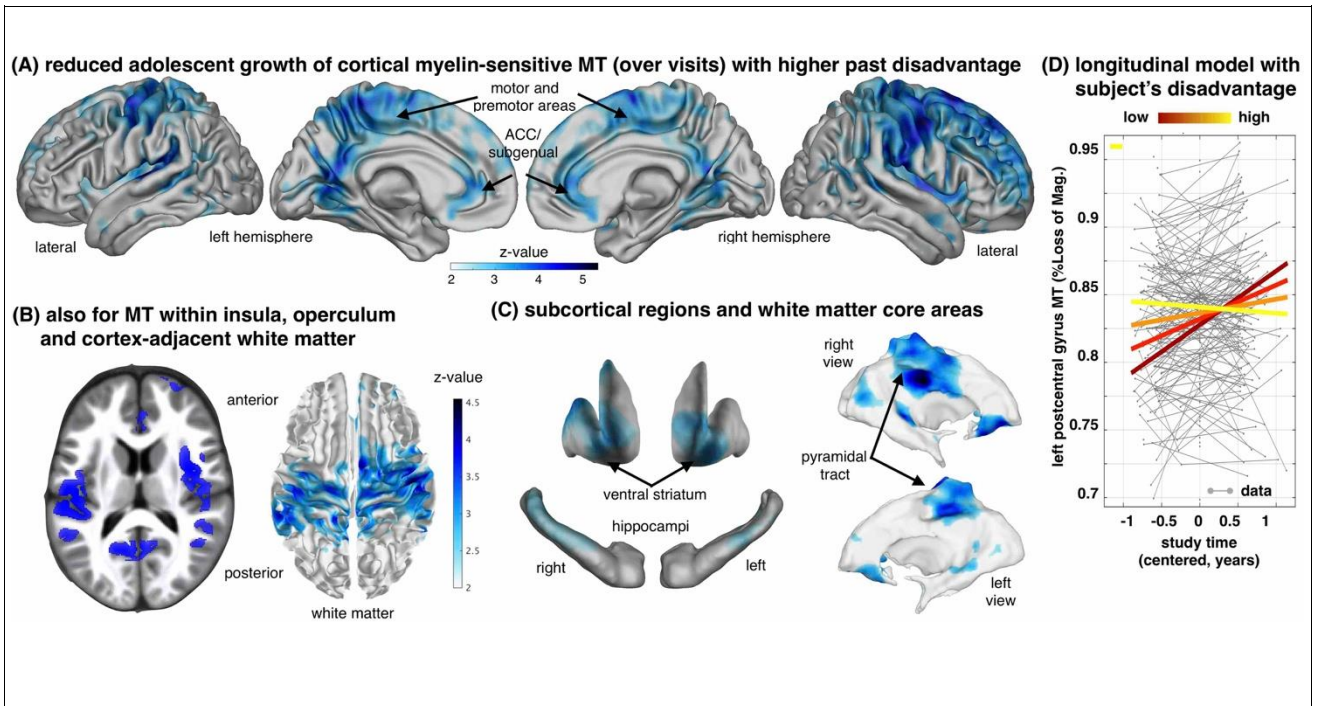
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**Figure 1. Socio-economic disadvantage (SED) during childhood is associated with slower myelin-related MT growth during coming of age.** **A.** Age-typical growth slows down with worsening early life SED in cortex, especially in bilateral precuneus/posterior cingulate, sensory-motor, premotor, sub-genual, and prefrontal areas (z-maps showing negative SED by time/visit interactions,  $p < .05$  FDR corrected,  $N=328/185$  scans/subjects in A-C, 45.7% female). **B.** MT growth is also reduced in insula, operculum (left) and the white matter adjacent to the affected cortex (right). **C.** Hippocampal and striatal grey matter, and core white matter regions also showed reduced growth of MT. **D.** SED-dependent rate of MT growth over visits in a region-of-interest sphere encompassing the central operculum/posterior insula (radius 6mm, centre at  $x=-47$ ,  $y=-22$ ,  $z=13$  mm, MNI). Plot shows subjects with higher SED (light yellow) compared to low SED subjects (dark red) express significantly less MT growth over visits (coloured lines in right panel indicate the interaction effect; y-axis: MT; x-axis: time of scan in years relative to each subject's mean age over visits).

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### 143 **The contribution of family factors**

144 How early life SED influences brain myelination is likely to involve family-related factors, indexed  
145 both by demographic characteristics but also how parents look after their children (Whittle et al.,  
146 2017). We examined whether parental education, parental occupation (a proxy for family income),  
147 and self-report measures of parenting quality accounted for the effect of SED on myelin growth  
148 trajectories (Ronfani et al., 2015; Sarsour et al., 2011). Parental educational qualifications were  
149 translated to years-of-education to derive a continuous measure. This variable partially accounted  
150 for our MT findings, broadly replicating but also expanding upon existing findings (Noble et al.,  
151 2015). Specifically, while peak clusters remained significant, their extent was much reduced,  
152 especially in the medial surface of the brain. For example, the left subgenual, right medial motor and  
153 right posterior cingulate clusters were largely abolished (cf. Figure 2A vs. Figure 1A). Therefore  
154 parental education appears to index influences overlapping with neighbourhood-level SED, but  
155 further important influences operate within SED. Against our hypothesis, controlling for poorly paid  
156 parental occupation (“Standard Occupational Classification: SOC2000 | HESA,” n.d.) without other  
157 family covariates had little impact on the relationship between SED and myelination (Figure 2B).

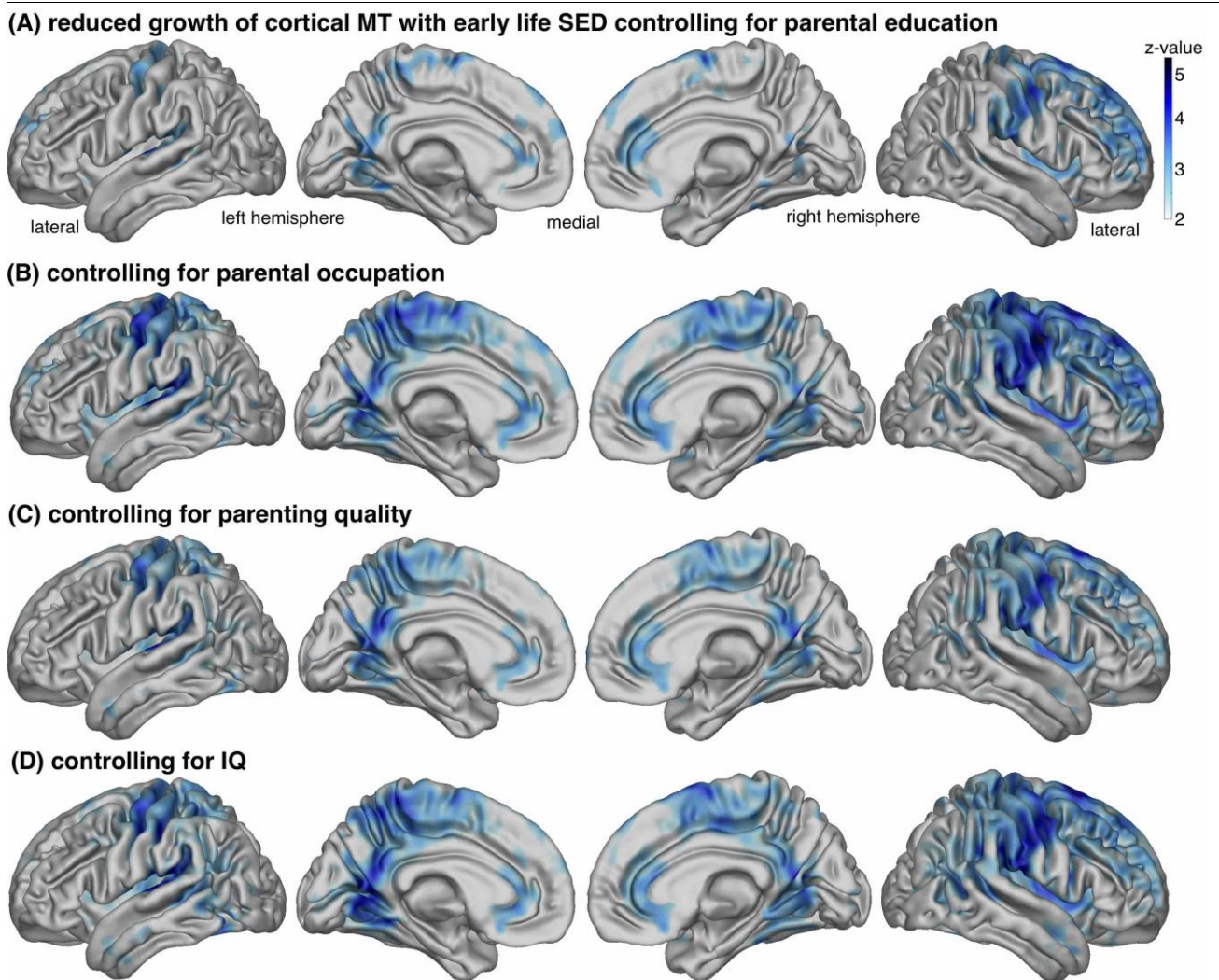
158 We next examined family factors proximal to the experience of participants, specifically subjectively  
159 reported parenting quality. Here, we used overall parenting quality as an independent variable,  
160 estimated by subtracting scores of negative parenting (e.g. harsh parenting or neglect) from those of  
161 positive ones (e.g., parental warmth or praise; see Methods). Component negative and positive  
162 scores were derived from three self-report questionnaires (Kiddle et al., 2017). We found that  
163 parenting quality was not associated with MTr and thus could not mediate the effect of SED on MTr  
164 (Figure 2C).

165 By contrast to the absence of mediation effects, we found a significant moderating effect of  
166 parenting on SED, such that better parenting significantly reduced the detrimental effect of early life  
167 SED on adolescent MTr. This expands upon existing studies (Sheikh et al., 2014; Whittle et al., 2017).  
168 Topographically, this moderating effect was largely confined to lateral prefrontal cortical MT (Figure  
169 3B) and subcortical MT (Supplementary table 3). Thus SED and parental education index overlapping  
170 psychobiological influences, while improved parenting quality indexes a separate influence whose  
171 presence might have a protective effect in more adverse environments.

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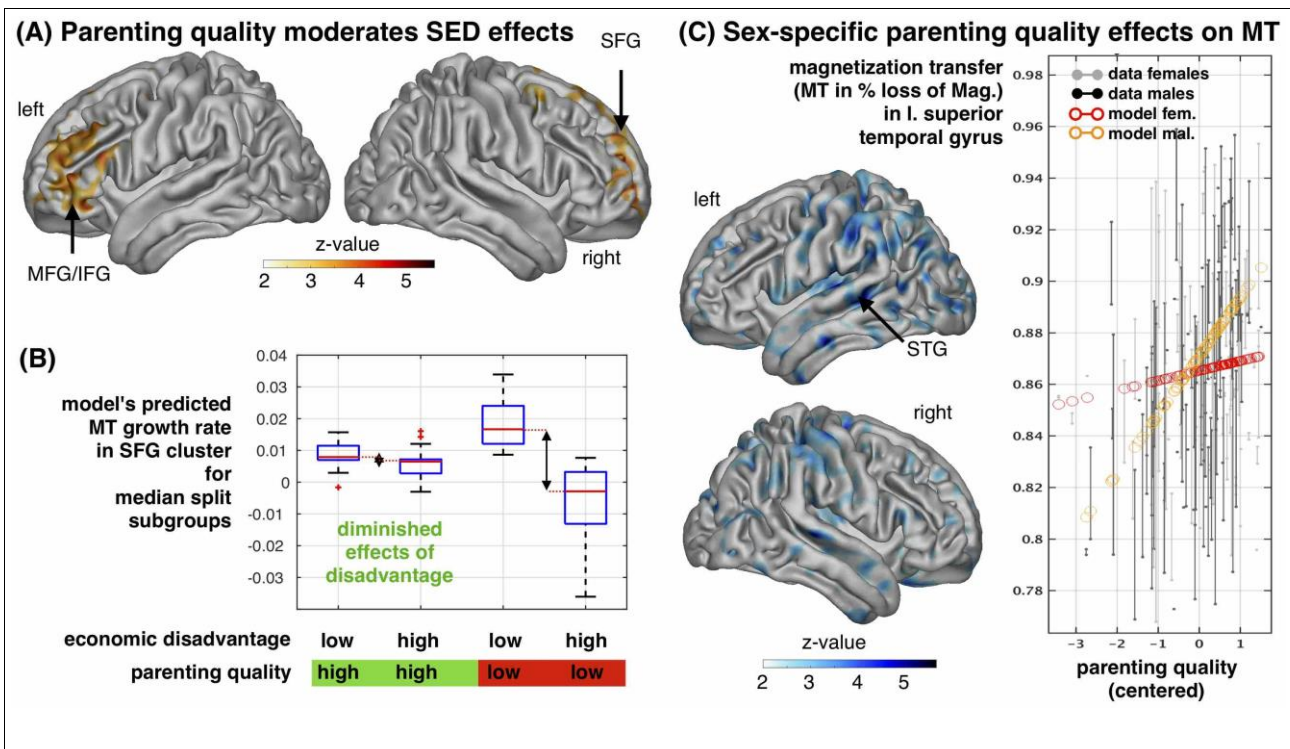
**Figure 2. Slower growth of myelin-sensitive MT as early life SED increases is partially explained by parental education but not other factors.** We present z-maps showing negative SED by time/visit interactions,  $p < .05$  FDR corrected,  $N=328/185$  scans/subjects, 45.7% female, when additionally controlling for multiple covariates and their respective time/visit interactions in A-C). **A.** Controlling for parental education reduces the impact of SED, in medial motor and premotor areas more than right lateral prefrontal ones (cf. Figure 1A) **B.** In contrast, controlling for parental occupation has minimal impact. **C.** Overall parenting quality has small impact (cf. see Figure 3). **D.** Controlling for time-varying IQ raw scores (here, WASI matrix) has negligible effect on the interaction (similar results for vocabulary, not shown). Controlling for baseline (or mean) IQ over the study period had a very similar effect. Colour scale is identical for A-D.

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**Figure 3. The effect of parenting quality on cortical myelin-sensitive MT and its interaction with SED. A.** Positive parenting moderated (in the sense of diminishing) the detrimental effect of socio-economic deprivation on prefrontal MT growth. Z-maps show a positive parenting quality by SED by time/visit interaction,  $p < .05$  FDR corrected. **B.** Illustration of the moderation effect (A.) within right superior frontal gyrus cluster. We show growth rates (MTr) as predicted by the longitudinal model within median split groups of high vs. low SED and high vs. low parenting quality. The box plot shows averaged data within 6mm sphere around peak voxel illustrating SED by time and parenting by SED by time/visit interaction. Early life SED effects on MTr (illustrated by arrow) are less pronounced in family contexts with high parenting quality. **C.** The effect of parenting quality on MT was significantly steeper in males compared to females (see also Supplementary table 4). Z-maps show negative sex by parenting quality interactions,  $p < .05$  FDR corrected,  $N = 328/185$  scans/subjects in A-C, 45.7% female, accounting for age, visit/time, sex, interactions and confounds. The right panel plots MT in superior temporal gyrus (6mm sphere around peak voxel) over parenting quality (x-axis, z-scored) and with adjusted data (grey/black) and model predictions (red/orange, effects of interest: intercept, parenting, sex by parenting). Higher parenting quality only showed a trend towards a positive main effect on cortical MT ( $p < .001$ , unc., not shown).

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### 179 Individual risk factors

180 A number of factors measured at the level of the individual might form either important causal  
 181 contributors, outcomes or markers for the association between SED and MTr. We predicted that  
 182 lower IQ would be associated with altered patterns of myelination consequent upon SED for three  
 183 reasons. First, prior evidence suggests that IQ might be related to individual differences of  
 184 myelination (Dunst, Benedek, Koschutnig, Jauk, & Neubauer, 2014). Second, there is evidence that  
 185 IQ and socio-economic status share similar genetic determinants (Trzaskowski et al., 2014). Thus,  
 186 genes that directly contribute to parental socio-economic success may also directly contribute to  
 187 differences of brain structure, as indexed by IQ. In other words, SED and brain growth could be  
 188 associated through horizontal genetic pleiotropy (Supplemental Figure S3). Third, the correlation



189 between socio-economic indices and IQ might be explained by morphometric brain measures  
190 (McDermott et al., 2019). To test the hypothesis that IQ would index biological processes largely  
191 overlapping with those present in SED, we controlled for verbal and matrix IQ scores (Figure 2D),  
192 both separately and as a total score. However, accounting for IQ in any of these ways left the  
193 relationship between SED and slower MTr unchanged.

194 We also examined the effects of self-reported ethnicity and alcohol drinking, as these are thought to  
195 be reflected in brain structure and connectivity (Noble et al., 2015; Smith et al., 2015). These failed to  
196 account for our key findings (Supplementary Figure S4A-B).

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198 We were interested whether determinants of poor physical condition, such as sedentary habits and  
199 poor quality nutrition, at least as indexed by body mass index (BMI), explained why more deprived  
200 children had lower MTr during adolescence. Thus, we tested a prediction that an association of MT  
201 trajectories with early life SED would be partially accounted by an increased BMI. This is important as  
202 both SED and poor parenting (Sleddens, Gerards, Thijs, Vries, & Kremers, 2011) increase the risk of  
203 being overweight (Salmasi & Celidoni, 2017), which is in turn associated with deviant white matter  
204 development (Kullmann, Schweizer, Veit, Fritsche, & Preissl, 2015).

205 Mean BMI was positively associated with early SED and negatively to MTm but not MTr, and did it  
206 account for the relationship between SED and MTr. As expected BMI increased with age during  
207 adolescence, but, importantly, it increased faster the greater the degree of early SED (Figure 4A).  
208 Correcting for age, and variables of no interest (see Methods), greater BMI was associated with lower  
209 MTm in anterior insula, anterior cingulate and other areas (Figure 4B and 4C). The relationship was,  
210 significantly more pronounced in males.

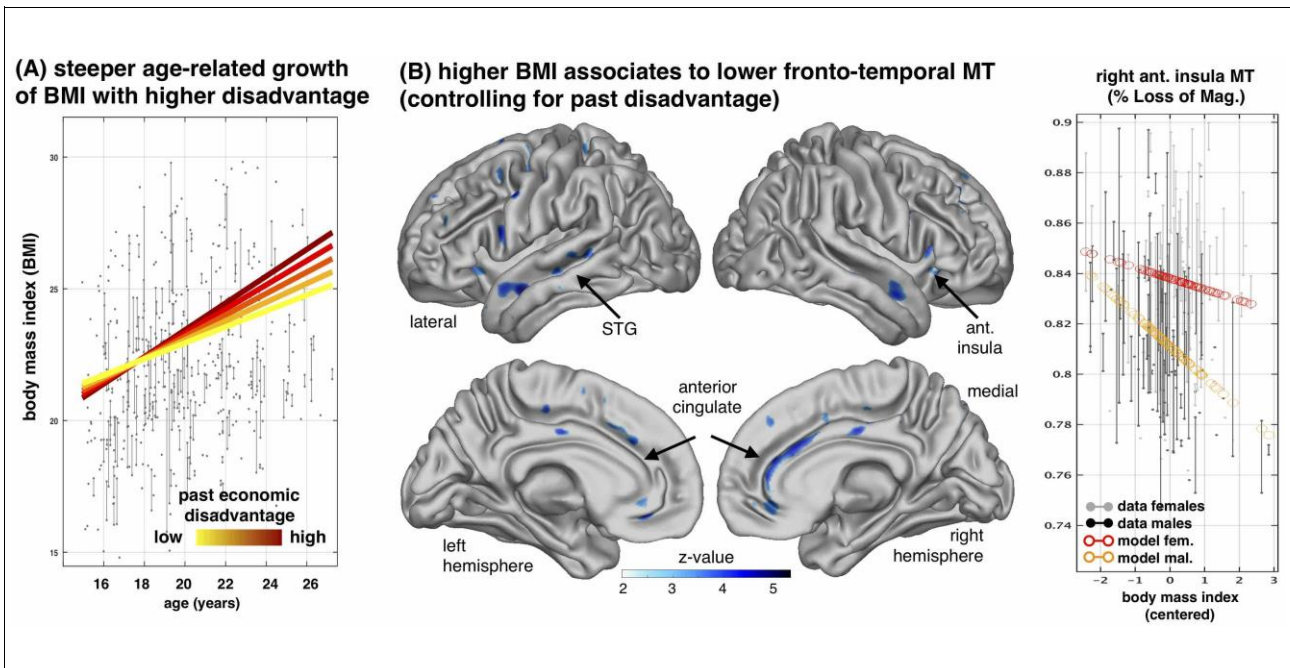
211 Lastly, we found no significant correlations between SED and global morphometric measures reported  
212 in large published studies (Johnson et al., 2016) (Figure S5).

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**Figure 4. The effect of body mass index on myelin growth. A.** Early life SED is associated with faster gain of body mass index (BMI) during youth. Linear-mixed modelling revealed positive age effects on BMI ( $t=4.6$ ,  $p=3.9e-6$ , two-tailed,  $df=559$ ), positive main effects of early life SED on BMI ( $t=2.05$ ,  $p=.0407$ , two-tailed,  $df=559$ ,  $N=568/384$  observations/subjects) and a steeper age-related increase with higher SED ( $t=2.2$ ,  $p=.0265$ ,  $df=559$ , two-tailed), accounting for age, visits, sex, and interactions. **B.** Greater BMI is associated with lower cortical myelin-sensitive MT in the anterior cingulate, superior temporal, anterior insula cortex (z-maps showing BMI effects,  $p<.05$  FDR corrected,  $N=277/155$  scans/subjects, 47.5% female, accounting for age, visit/time, sex, early life SED, interactions and confounds). **C.** Right panel shows the plot of MT in insula (6mm sphere around peak voxel) over BMI (x-axis, centred) and with adjusted data (grey/black) and model predictions for sexes (red/orange, effects of interest: intercept, BMI, sex by BMI). The decline of MT with higher BMI is steeper in males than females. See also Supplementary Table 5.

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## 219 Discussion

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221 We studied the relationship of early socio-economic disadvantage to myelin growth during  
222 adolescence, de facto a relationship between economic disadvantage and deviant neurodevelopment  
223 (Johnson et al., 2016). Early disadvantage correlated with a globally reduced myelin and reductions in  
224 myelin growth longitudinally, as indexed by the sensitive marker magnetization transfer saturation,  
225 MT. Reminiscent of other developmental findings (Sheikh et al., 2014; Whittle et al., 2017), parental  
226 education, but not other predictors, accounted statistically for much of this effect. Better parenting  
227 moderated the relationship, lessening the effect of economic disadvantage. As hypothesized,  
228 increased BMI also indexed deficits in myelin development. However, although BMI was robustly  
229 related to SED, BMI had an effect on myelination independently of SED (and not explaining it). These  
230 findings have important implications for further, translational research and are relevant to protecting  
231 brain development during youth as we shall see.

232 As our sample was healthy, slower myelination constituted neurodiversity rather than  
233 neuropathology. Diversity can be seen as biologically encoding prior beliefs (Dayan, 2012; Moutoussis  
234 et al., 2018) conferring adaptation, maladaptation (Jensen et al., 2017) or both, depending on  
235 functions yet to be studied. On the one hand, the fact that we observed only reductions in MTr, that  
236 these were very extensive, and that they were related to early but not current SED, suggest  
237 maladaptation, at least with respect to current circumstances.

238 Parental education substantially mediated the effects of SED (Figure 2), suggesting these two  
239 processes index overlapping biological pathways, reducing MTr. Remarkably, according to our results  
240 this is unlikely to be due to IQ-related genes, to parenting quality as perceived by the young person,  
241 over-weight, alcohol drinking or ethnicity. It is thus important to further understand what (non-IQ)  
242 genes or proximal environmental drivers underpin different myelination trajectories. These may be  
243 diverse and could include different parental behaviours not captured by our measure of parenting,  
244 the provision of enriched primary schooling, other family environment factors such as parental  
245 conflict, or factors associated with early peer processes.

246 Early poverty is associated with lower life achievement and IQ (Evans & Cassells, 2014) and brain  
247 structure may mediate this at least in part (McDermott et al., 2019). In our study, however, baseline  
248 IQ scores did not account for the effect of SED. We note that previous research often directly  
249 incorporated parental education as a measure of SED, and this may itself strengthen the relation  
250 between IQ and SED. Our findings imply that genes directly contributing to both (neighbourhood) SED  
251 and MT growth do not underpin our IQ measures. However, SED-dependent vertical pleiotropy may  
252 operate. Here, genetic or indeed environmental antecedents would give rise to an intermediate  
253 phenotype, on which SED influences would operate to affect neurodevelopment. In this case SED  
254 would disproportionately affect the genetically vulnerable (Gage, Smith, & Munafò, 2016). Vertical  
255 pleiotropy is further explained in Figure S3.

256 Primate experiments show that early stressors (Howell et al., 2013) cause long-term problems,  
257 including an impact on brain myelination. By analogy, early developmental stressors are likely to be  
258 commoner among disadvantaged children. However here, unlike in animal studies, diffuse low-impact  
259 mechanisms rather than focal, high-impact ones are more likely to account for the relationship  
260 between SED and myelination. This is because the sample was healthy, and severe adversity was  
261 under-represented (Figure S1). If broad low-impact influences operate, future research should also  
262 prioritize broad influences and interventions over searches for focal, high-risk subgroups.

263 In primate variable foraging demand (VFD) experiments, it is resource insecurity (Coplan et al., 2006),  
264 rather than the average resource level, that affects infant neurodevelopment, suggesting that  
265 neighbourhood SED may index stressful economic insecurity for all, not just the poor, consistent with  
266 parental occupation not accounting for the effect of SED. That VFD effects may be mediated by  
267 maternal preoccupation by insecurity (Coplan et al., 2006) would be consistent with positive parenting  
268 modestly mitigating the effects of SED (Figure 3).

269 We did not replicate a number of findings in the literature connecting SED to macroscopic measures  
270 such as grey matter volume or surface area. Our smaller sample, though a limitation, is likely to mean  
271 that the myelination effects are more prominent, so easier to detect. Results are also consistent with  
272 myelination not being straightforwardly reflected in macroscopic measures (Grydeland, Walhovd,  
273 Tamnes, Westlye, & Fjell, 2013).

274 One limitation of our study that future research should address, is that early SED was assessed  
275 retrospectively. Secondly, although chronological age is important, future studies should use  
276 endocrinologically precise pubertal stage as a developmental independent variable. Thirdly, studies  
277 should address more deprived populations in an international scale. SED influences on myelination  
278 may be studied in 'natural experiments', such as the precipitous, decade-long exposure to serious SED  
279 of Greek children born since 2010 across genetic, educational and occupational strata, resembling a  
280 powerful VFD manipulation.

281 Our research informs future research directions to knowledge about causation and to policies that can  
282 protect brain development in young people. First, the functional consequences of the slower  
283 myelination must be demonstrated. For example, adverse effects of high BMI on mid-life cognitive  
284 function may be restricted to disadvantaged groups (Cohen-Manheim et al., 2017). How SED  
285 dependent myelination longitudinally impacts on IQ and on specific sensory-motor, emotional and  
286 cognitive functions (Sheehy-Skeffington & Rea, 2017) remains unclear and deserves research  
287 attention. Most importantly, our findings indicate that intervention studies aiming to reduce SED  
288 and/or improve parental education and parenting in richer countries should prospectively examine  
289 their impact on myelination.

290 In conclusion, neighbourhood deprivation during development was associated with slower myelin  
291 growth markers during adolescence and young adulthood. This was independent of baseline IQ,  
292 ethnicity or parental occupation, while parental education statistically explained much of the effect  
293 and may give clues about causal mechanisms. Causation, functional consequences of myelination and  
294 policy implications provide a fertile context for future investigations.

## 295 **Materials and Methods**

### 296 **Recruitment, demographic and psychological measures**

297 Participants were recruited from the Neuroscience in Psychiatry network participant pool (Kiddle et  
298 al., 2017). From this pool, also known as the '2K sample', 300 participants were recruited for the  
299 present scanning study. We aimed to exclude all but the most minor psychiatric and neurological  
300 symptomatology, and therefore screened by self-report participants to not have current or previous  
301 relevant medical histories. We finally analysed 497 available brain scans from 288 healthy (149 female)  
302 individuals that passed quality control. In particular, data from 100, 167, and 21 subjects with one,  
303 two or three visits per person were available, with mean (standard deviation) follow-up interval of 1.3  
304 (0.32) years between first and last visit.

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306 Self-defined ethnic group was asked about shortly after recruitment and in terms of the following  
307 broad classes: White (1858 or 80% of declared ethnicity), Black (3.7%), Asian (8.5%) Mixed (6.0%),  
308 Other (2.1%), 'Prefer not to say'. On the day of scanning, participants also completed the Wechsler  
309 Abbreviated Scale Intelligence of (WASI) (Kiddle et al., 2017). As ours was a developmental study, we  
310 used the raw subscale scores for vocabulary and matrix IQ and explicitly analysed, and their  
311 dependence of age. Unless otherwise stated, IQ measurements refer to the time of the first, 'baseline'  
312 scan.

313 The measure of overall parenting quality that we used here was a composite of the Positive Parenting  
314 Questionnaire (PPQ), Alabama Parenting Questionnaire (APQ) and Measure of Parenting Style  
315 (MOPS). All three were obtained within about a month of the first scan (Kiddle et al., 2017). We took  
316 the reversed positive parenting total score from the PPQ and the similarly reversed positive parenting  
317 scales from the APQ, the negative parenting scales from the APQ (inconsistent discipline, poor  
318 supervision, and corporal punishment) and the negative parenting scores for the MOPS (abuse, control  
319 and neglect), which were standardized and summed to make a composite negative parenting scale.  
320 The internal consistency of the resulting total score was  $\alpha = .96$ .

321 As far as parental education is concerned, the young people in our study reported the highest  
322 qualification and occupational level of their parents. This data was obtained for the mother, the father,  
323 and if applicable the mother's partner and the father's partner. These were converted to an ordinal  
324 scale, according to a categorization of educational achievement in England - that is, none, primary  
325 school, secondary school - GCSE's, sixth form - A levels, skills-based trainings, undergraduate  
326 education, postgraduate education or higher professional training. We then took as starting score the  
327 education level of the female parent (usually biological mother) and compared it with the primary  
328 male parent (mother's partner or biological father, in that order of priority). It was unusual for these  
329 to differ by more than one on this ordinal scale. Therefore, if only one parent score was available, we  
330 used that for 'parental education'; otherwise we averaged the two prioritized scores.

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### 332 **Measures of Socio-Economic Disadvantage**

333 We used the following measures of socio-economic disadvantage. As our central measure, we used  
334 the neighbourhood proportion of households below the official poverty income around the



335 participant's residence ("Small area model-based households in poverty estimates, England and Wales  
336 - Office for National Statistics," n.d.) at the time of first scan. We also used an index of parental  
337 education (IPE); and the mother's and father's SOC2000 occupational class ("Standard Occupational  
338 Classification: SOC2000 | HESA," n.d.).

339

#### 340 **MRI data acquisition and longitudinal preprocessing**

341 Brain scans were acquired using the quantitative MPM protocol (Weiskopf et al., 2013) in 3T Siemens  
342 Magnetom TIM Trio systems located in Cambridge and London. Isotropic 1mm MT maps were  
343 collected to quantify local myelin changes throughout the brain. Analyses were performed using  
344 SPM12 (Wellcome Centre for Human Neuroimaging, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>),  
345 the h-MRI toolbox for SPM (Draganski et al., 2011) [[https://github.molgen.mpg.de/hMRI-](https://github.molgen.mpg.de/hMRI-group/Toolbox)  
346 [group/Toolbox](https://github.molgen.mpg.de/hMRI-group/Toolbox)], Computational Anatomy toolbox (CAT12, <http://www.neuro.uni-jena.de/cat/>) and  
347 the tools described in more detail below and in the methods section of the preceding paper that  
348 focussed on effects of demographics in the same sample (Ziegler et al., 2018).

349

350 To assess macromolecular growth during development, we used a longitudinal Voxel-Based  
351 Quantification (VBQ) pipeline that follows the following steps (for more details and illustration see  
352 Ziegler et al., 2018). First, images were serially registered. Each baseline - follow-up mid-point image  
353 was then segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (using the  
354 CAT12 toolbox of SPM). MT maps from all time-points were then normalized to MNI space, manually  
355 inspected and checked for outliers. A during scan motion proxy was used to discard 10% of images  
356 with strongest motion-induced artefacts and as a confounding covariate during all analyses. We  
357 constructed masks for both grey and adjacent white matter using SPM neuromorphometrics atlas for  
358 tissue-specific analysis of MT parameters. Finally, normalized MT maps were processed with a tissue-  
359 weighted smoothing procedure (7 mm FWHM).

360

#### 361 **Longitudinal MT image analyses**

362 In order to quantify myelin development we took advantage of the observational accelerated  
363 longitudinal design. We focused on how the brains change over study time/visit. We compared and  
364 contrasted this to how brain structure varied with scan-midpoint age across participants in the study.  
365 To do so, we used the Sandwich Estimator (SwE) method for voxel-based longitudinal image analysis  
366 (Guillaume et al., 2014, <http://www.nisox.org/Software/SwE/>). This so-called marginal model  
367 describes expected variability as a function of predictors in a design matrix, while additionally  
368 accounting for correlations due to repeated measurements and unexplained variations across  
369 individuals as an enriched error term.

370 In our analyses, we focused on factors time/visits and mean age of the individual (over all visits) on  
371 MT across the whole brain. To investigate how exposure to poverty was related to brain trajectories  
372 and altered growth, we enriched the models by adding a main effect (SED as measured by the NPI, as  
373 a predictor of mid-point MT) as well as the interaction of SED with individual MT change over scan  
374 sessions (visits or within-subject study time). The latter metric allowed us to assess how myelin growth  
375 is associated with SED (e.g. lower myelin growth upon exposure to high SED), whereas the former

376 indicates how SED relates to overall myelination differences across individuals accounting for other  
377 covariates, such as visit, mean age, and sex. We a-priori hypothesized reduced levels of myelin and  
378 impaired myelin growth with higher SED. The effects of visit, age, sex, and non-linearities (e.g. in terms  
379 of age by age and age by time interactions) of age-related trajectories, and for first order interactions  
380 among all demographic variables are presented elsewhere (Ziegler et al., 2018). All analyses were  
381 carried out with scanning site, total intracranial volume and motion regressors as confounds. More  
382 mathematical details on SwE and longitudinal design specification can be found in supplementary  
383 information of Ziegler et al., 2018.

384 We then tested whether the observed associations of SED might be explained by further covariates,  
385 by including the latter on the same footing as SED in analyses. All models were tested for indications  
386 of effects of sex, IQ, parental education, parental occupation and self-reported ethnicity. We further  
387 conducted moderation analysis in terms of indications whether above family or individual factors  
388 show a significant interaction with SED either on mean level MT or MT growth over visits. Thus, two-  
389 way interaction with SED (e.g. parenting quality by SED) and three-way interaction terms (e.g.  
390 parenting quality by SED by time/visit) were included in addition to all main effects, time, age, sex,  
391 and their interactions in SwE models of local MT. We controlled for the False Discovery Rate (FDR,  
392  $p < .05$ ) during corrections for multiple comparisons in all image analyses.

393

#### 394 **Linear mixed effects modelling of global MT and BMI**

395 To assess the effects of SED on global MT and on BMI, we used linear mixed-effects modelling (LME,  
396 cf. supplementary information Ziegler et al., 2018). We specified corresponding fixed effects design  
397 matrix including time, age, sex, SED, and first order interactions while accounting for confounds.  
398 Random-effect intercepts were included and proved optimally suited using likelihood ratio tests. T-  
399 values of fixed effects coefficients and corresponding (one-sided) p-values were calculated to test for  
400 detrimental main effects of SED and time/visit or age interactions. More mathematical notes on LME  
401 and longitudinal design specification can be found in supplementary information of Ziegler et al., 2018.

402

403

#### 404 **Macrostructural measures**

405 Finally, to complement the main focus of this study in assessing SED-related correlates of novel,  
406 quantitative, myelin-sensitive MT (using VBQ), we also tested for previously reported relationships of  
407 SED with conventional metrics, i.e. Voxel-Based and global Surface-based Morphometry (VBM &  
408 SBM). For this purpose we used non-linear registration to obtain normalized (grey and white matter)  
409 tissue segment maps using both within- and between-subjects modulation. This was followed by  
410 Gaussian smoothing (6mm). Moreover, cortical surface reconstructions of all participants' midpoint  
411 was obtained (using CAT Toolbox), and cortical thickness, surface area, gyrification index, and sulcal  
412 depth was assessed in native space, resampled to a surface template and smoothed with 12mm.

413

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#### 425 **Competing Interests**

426 E. Bullmore is supported by and holds stock in GlaxoSmithKline Ltd. The other authors have no  
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