

1 **Impact of second-generation antipsychotics on white matter microstructure in**
2 **adolescent-onset psychosis.**

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28 **Abstract**

29 White matter abnormalities are well-established in adult patients with psychosis. Yet less is
30 known about changes in early onset psychosis (EOP) during adolescence, especially whether
31 antipsychotic medication might impact white matter microstructure in this sensitive phase. Here,
32 we utilized Magnetic Resonance Imaging (MRI) in unmedicated and medicated adolescent
33 EOP patients in comparison to healthy controls to examine the impact of antipsychotic
34 medication status on indices of white matter microstructure. Twenty-two EOP patients (11
35 unmedicated) and 33 healthy controls, aged between 12-18 years, underwent 3T diffusion-
36 weighted MRI. Using Tract-based Spatial Statistics, we calculate case-control differences in
37 scalar diffusion measures, e.g. fractional anisotropy (FA), and investigated their association
38 with antipsychotic medication. We replicated previous results from studies in EOP patients
39 showing significantly decreased mean FA including the left genu of the corpus callosum, the
40 left anterior corona radiata and the right superior longitudinal fasciculus in patients relative to
41 healthy controls. Mean FA in the left anterior corona radiata was significantly associated with
42 antipsychotic medication status, showing higher FA values in medicated compared to
43 unmedicated EOP patients. Increased regional FA values might be a first hint towards an early
44 effect of antipsychotic medication on white matter microstructure in adolescent EOP patients.

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55 Introduction

56 A variety of hypotheses has been proposed to explain the etiology of psychotic disorders,
57 including aberrant dopamine neurotransmission ¹, altered neurodevelopmental trajectories ²,
58 and active neuroinflammation ³. Such theories are not mutually exclusive and are more likely
59 complementary. Patients with early onset psychosis (EOP), with defined age of onset before
60 18 years, provide an unprecedented opportunity to specifically investigate the perspective of
61 aberrant neurodevelopment.

62 The application of diffusion weighted imaging (DWI) can relate white matter organization to
63 disease. DWI maps the Brownian movement of water molecules in the brain in vivo, and as
64 axon membranes and myelin provide natural barriers for water diffusion, DWI can be used to
65 infer local tissue properties ⁴. The most commonly used scalar measure is fractional anisotropy
66 (FA), which characterizes the degree of diffusion directionality. For an in-depth evaluation of
67 FA, the relative contribution of axial diffusion (AD) along the primary axis, and radial diffusion
68 (RD) perpendicular to it, can be informative. RD has been associated with changes in myelin
69 ⁵, and a disruption of myelin sheaths may be reflected in an increased RD. Conversely, AD
70 has been linked to axonal integrity and axonal damage may be characterized by decreased
71 AD ⁴.

72 Using DWI, a number of studies show widespread FA reductions in many different brain
73 regions with low spatial overlap such as corpus callosum, cingulum, superior longitudinal
74 fasciculus, inferior longitudinal fasciculus and fronto-occipital fasciculus in EOP patients
75 compared to healthy controls ⁶⁻¹⁰. Scalar DWI measures beyond FA are rarely analyzed in EOP
76 populations. However, Lagopoulos and colleagues report on increased RD values, indicative
77 of potential demyelinating processes underlying the observed white matter abnormalities ¹⁰.

78 The low degree of regional specificity of white matter changes seems to be attributed to a
79 number of factors including differences in image acquisition, different analysis approaches
80 (ROI vs voxel-wise), small sample sizes, low prevalence of EOP (estimated prevalence of 17.6
81 in 10,000 at age of 18 years, ¹¹) and differing sample characteristics such as age of onset.
82 Further, antipsychotic medication status might also affect the pattern of white matter
83 microstructure in EOP.

84 Studies investigating white matter microstructure in EOP mainly focus on case-control
85 differences, either reporting antipsychotic effects as secondary findings or using antipsychotic
86 medication status as a covariate of no interest. So far, studies in EOP patients do not indicate
87 an impact of either current ¹²⁻¹⁴ or cumulative antipsychotic exposure ^{6,13,15} on scalar DWI
88 measures. The absence of an antipsychotic medication effect could reflect small sample sizes

89 and young patients with shorter medication histories. The apparent limitations of the
90 adolescent study population also hold potential advantages: EOP patients are less affected by
91 chronic exposure to antipsychotic medication in comparison to their adult counterparts, which
92 allows for dissecting medication-mediated from disease-related effects on brain structure.
93 Furthermore, according to the World Health Organization guideline for pharmacological
94 interventions in adolescents with psychotic disorders (2015), antipsychotic medication use is
95 significantly less recommended in comparison to adult patients with psychosis¹⁶. This partly
96 translates to a clinical practice of a higher reluctance in starting antipsychotic treatment early
97 in the course of psychosis in children and adolescents, leading to a higher percentage of
98 antipsychotic-naïve EOP patients relative to adult first episode patients with psychosis. Thus,
99 EOP patients represent an ideal population to investigate the impact of antipsychotic
100 medication on white matter structure early in disease progression.

101 Here, we use a thoroughly clinically characterized adolescent EOP sample to (1) investigate
102 white matter microstructure in comparison to healthy controls, and (2) explore the association
103 between second-generation antipsychotic medication and white matter microstructure in
104 medicated compared to currently unmedicated/antipsychotic-naïve EOP patients. We utilize
105 DWI and, by using Tract-Based Spatial Statistics (TBSS), we calculate FA and its scalar sub-
106 measures, RD and AD, and investigate their association with antipsychotic medication and
107 other clinical measures (e.g. Positive and Negative Syndrome Scale, etc.). Based on the
108 existing literature, we hypothesized that EOP patients show widespread reduced FA attended
109 by increased RD and unchanged AD compared to healthy controls, mainly in the corpus
110 callosum and superior/inferior longitudinal fasciculus. As there are no established effects of
111 antipsychotic medication on white matter structure in EOP patients, our post hoc analysis is
112 exploratory by nature.

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119 **Results**

120 ***Demographic and clinical data***

121 As presented in Table 1, EOP patients did not differ significantly from controls in general
122 demographic variables such as age, handedness and IQ. However, there was a significant
123 case-control difference in clinical measures such as CGAS and MFQ, reflecting the clinical
124 diagnosis. EOP patients showed higher impairment of general functioning evaluated with
125 CGAS and exhibited significantly more depressive symptoms using MFQ, relative to their
126 healthy counterparts. Furthermore, patients report significantly more cannabis use than
127 controls.

128 Within the patient group (Table 2), patients on antipsychotic medication were significantly older
129 than unmedicated patients ($t = -4.186$, $p = 0.0006$). In line with antipsychotic medication status,
130 duration of untreated psychosis (DUP) was significantly longer in the unmedicated EOP
131 subgroup in comparison to the medicated group. Further demographic and clinical variables
132 did not differ significantly between the patient subgroups.

133 ***TBSS analyses***

134 Voxel-wise statistical analysis of case-control differences revealed decreases in mean FA
135 including the left genu of the corpus callosum, the left anterior corona radiata (ACR), and the
136 right superior longitudinal fasciculus (SLF) in EOP patients compared to healthy controls (see
137 Figure 1 and Table 3). There was no increase in mean FA for the opposing contrast.

138 Applying the TBSS pipeline to diffusion-derived data other than FA, namely RD and AD, did
139 not yield significant case-control differences for RD, but decreases in mean AD overlapping
140 with FA findings in EOP patients in comparison to healthy controls. In detail, mean AD shows
141 significantly decreases in the left ACR (see supplementary Table S2), in addition to decreases
142 in the right posterior limb of the internal capsule (PLIC) and right superior fronto-occipital
143 fasciculus (SFOF).

144 Extracted mean values of all scalar diffusion measures for all significant clusters stratified by
145 group are displayed in supplementary Figure S1 for descriptive purposes only. In the interest
146 of transparency, TBSS case-control differences in mean FA and mean AD (patients < controls)
147 at a cluster-forming threshold of $p \leq 0.05$ are also presented (see supplementary Figure S2).

148 ***Linear regression analyses***

149 To evaluate the potential influence of duration of illness and antipsychotic treatment on regional
150 mean FA and mean AD values within significant TBSS clusters, in patients, linear regression

151 analyses were performed. While duration of illness was not significantly associated with mean
152 FA in any of the clusters, we found a significant negative association with mean AD in the left
153 ACR ($t = -2.364$, $p = 0.029$). For latter association, however, the regression equation was not
154 significant ($p = 0.085$) and the overall explanatory power of the model was low ($R^2 = 0.147$),
155 rendering this finding most likely spurious (see supplementary Table S1).

156 Exposure to antipsychotic medication was significantly associated with mean FA values in the
157 left ACR ($t = 2.991$, $p = 0.008$), showing higher mean FA in medicated relative to the
158 unmedicated patients (Figure 2). There was no association between antipsychotic medication
159 and mean FA or mean AD in the other significant TBSS clusters (see supplementary Table
160 S1). Cohen's d effect size values suggest a high ($d = 1.48$) and a low ($d = -0.08$) standardized
161 difference in mean FA of the left ACR in unmedicated and medicated EOP patients relative to
162 healthy controls, respectively (Figure 3). Based on visual inspection, higher mean FA in
163 medicated patients seems driven by an increase in AD and a decrease in RD (Figure 2).
164 However, mean AD and RD did not differ significantly between medicated and unmedicated
165 patients (Welch Two Sample t -test, AD: $t = 0.183$, $p = 0.857$; RD: $t = 1.887$, $p = 0.079$).

166 ***Association with clinical measures***

167 We found no association between current antipsychotic medication evaluated as
168 chlorpromazine equivalent at scan day (CPZ, Spearman $\rho = 0.13$, $n = 11$, $p = 0.695$) or
169 cumulative CPZ (Pearson $\rho = -0.15$, $n = 11$, $p = 0.665$) with regional mean FA values in the
170 left ACR.

171 In addition, we also found no significant correlations, which survived correction for multiple
172 comparisons (FA cluster: Bonferroni, $\alpha = 0.003$; AD cluster: Bonferroni, $\alpha = 0.004$), between
173 neither extracted mean FA nor mean AD values of all significant TBSS clusters and clinical
174 measures such as PANSS (neither positive nor negative), CGAS and MFQ scores.

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178 Discussion

179 Our case-control results replicate prominent brain regions with known white matter
180 abnormalities implicated in EOP, namely corpus callosum⁶, right SLF^{14,17,18} and the left ACR
181^{9,10}. Intriguingly, lower FA in these regions seems to occur early in the disease process^{10,18,19}.
182 For instance, Lagopoulos and colleagues found a decrease in FA in the left ACR in both
183 patients with established psychiatric disorder and patients exhibiting sub-syndromal symptoms,
184 aged 14-30 years. Based on these findings, the authors proposed that abnormalities in the left
185 ACR are a putative precursor to the development of a psychiatric condition¹⁰.

186 However, the ACR is a highly heterogeneous structure with three long-range association fiber
187 tracts traversing through it¹⁰: anterior thalamic radiation (ATR), inferior fronto-occipital
188 fasciculus (IFOF) and uncinate fasciculus (UF). All three association fibers form connections
189 to the frontal lobe and have been implicated in the pathophysiology of psychiatric disorders
190^{10,20-22}. In the current study, the left ACR peak voxel shows a 16% probability of IFOF
191 involvement based on the JHU White-Matter Tractography Atlas. The IFOF connects the
192 occipital and temporal lobes with the orbitofrontal cortex as part of the ventral visual and
193 language stream. In particular, the left IFOF seems to subserve language semantics²³. Already
194 in 1996, Aloia and colleagues proposed that the disruption of semantic networks have potential
195 implications for the origin of “thought disorder” in schizophrenia²⁴. Adding to this hypothesis,
196 patients with 22q11.2 deletion syndrome, who are genetically at high risk for developing
197 schizophrenia, showed lower FA values in left IFOF²⁵. Furthermore, DeRosse and colleagues
198 found that lower FA proximal to the SLF and corticospinal tract bilaterally, and left IFOF and
199 left inferior longitudinal fasciculus (ILF), were associated with higher levels of psychotic-like
200 experiences in otherwise healthy volunteers²⁶. In early-onset schizophrenia (EOS) patients,
201 lower FA in the left IFOF and the left ILF predicted worse neurocognitive performance⁹. The
202 authors also detected a shared decrease in FA in the left IFOF among patients with clinical
203 high risk for schizophrenia and patients with established EOS, in comparison to healthy
204 controls. Together, these findings suggest that white matter abnormalities in the left ACR,
205 putatively in the left IFOF, may represent a potential candidate for understanding the etiology
206 of psychosis.

207 This assumption seems further supported by effects of antipsychotic medication on diffusion
208 metrics in the left ACR. We found that FA values in the left ACR were significantly predicted
209 by antipsychotic medication status, with higher FA values in medicated relative to unmedicated
210 EOP patients. No such association was found with the other brain regions showing significantly
211 decreased FA values. Besides the high Cohen’s d effect size estimate (Figure 2), we found no
212 significant association of regional FA with either current or cumulative antipsychotic exposure.

213 This lack of significant associations is, however, in line with previous studies in EOP patients
214 ^{6,12-15} and likely due to the fairly short medication history in EOP patients compared to their
215 adult-onset counterparts or limited sample size. Hence, the presence of antipsychotic
216 medication rather than the actual dose might induce the observed changes in white matter
217 microstructure.

218 In medicated patients, increased FA values seem to be driven by an increase in AD and a
219 decrease in RD, relative to their unmedicated counterparts (Figure 2). Thus, FA might be
220 enhanced by antipsychotic medication as a result of both facilitated parallel diffusivity (AD,
221 potentially mediated by an increase in axon numbers, and restricted perpendicular diffusivity
222 (RD), indicative of changes in myelin.

223 Converging evidence from multiple studies suggests oligodendroglial dysfunction, with
224 subsequent abnormalities in myelin maintenance and repair, to underpin white matter
225 abnormalities observed in psychotic patients ²⁷. In the framework of schizophrenia, it has been
226 proposed that myelin dysfunction, especially in frontal regions, contributes to psychotic
227 symptoms ^{13,27}. Based on findings from cell culture studies using aripiprazole ²⁸ and rodent
228 work using quetiapine ^{29,30}, second-generation antipsychotic medication may promote
229 oligodendrocyte recovery and myelin repair leading to reduced white matter abnormalities and,
230 subsequently, reduced psychotic symptoms. A recent study in patients with schizophrenia also
231 reports on promyelinating effects of antipsychotics ³¹. Tishler and colleagues found an increase
232 in intracortical myelin predominantly mediated by risperidone and other second-generation
233 antipsychotics in adult patients with schizophrenia compared to healthy controls within the first
234 year of treatment. In the current study, given that medicated EOP patients received either
235 aripiprazole, quetiapine or risperidone, one might speculate that early medication with second-
236 generation antipsychotics might affect white matter microstructure by remediating
237 oligodendroglial dysfunction, leading to an increase in FA detected by DWI.

238 Even though FA is highly sensitive to microstructural changes in general, it lacks
239 neurobiological specificity to the exact type of change ⁴. For instance, a decrease in FA can
240 reflect alternations in fiber organization, including packing density and fiber crossing, and
241 myelin loss or myelin remodeling ³². We found a widespread decrease of AD on a whole brain
242 level, indicative of axonal damage, but no changes were found in RD, relative to healthy
243 controls. This finding is not in line with previous work from Lagopoulos and colleagues, who
244 found a decrease in FA in the left ACR associated with increases in RD and no changes in AD
245 ¹⁰.

246 Although there are likely several reasons for these conflicting findings, neuroinflammatory
247 processes might pose particular difficulties in interpreting DWI signals in psychotic populations

248 ³³. For instance, in an animal model of cuprizone-induced demyelination of corpus callosum,
249 regions with extensive axonal edema and prominent cellular inflammation showed no change
250 in RD, while AD values were diminished at the beginning of demyelination ³⁴. Given the
251 neuroinflammation hypothesis of schizophrenia ³, it seems likely that the disease progression
252 encompasses a dynamic evolution of inflammation, axonal injury, and myelin degeneration. In
253 the current study, one might speculate that EOP patients are on the verge of undergoing
254 demyelination processes, reflected by widespread decreases in AD. However, the timing of
255 neuroinflammation in psychotic disorders relative to tissue injury is unclear, leading to a
256 heightened risk of misinterpreting changes in DWI measures. According to a recent review of
257 Winklewski and colleagues, in cases of neuroinflammation linked to tissue damage, DWI
258 seems to underestimate the extent of demyelination (undervalued RD), and overestimate the
259 extent of axonal injury (overvalued AD) ³⁵. This pattern seems replicated in our study, with
260 significant changes in AD and no changes in RD. As the consistency of DWI metrics seems
261 affected by brain edema and inflammatory response, future studies can benefit from using
262 tools such as free water imaging which provide the opportunity to separate the contribution of
263 extracellular water from the diffusion of water molecules inside the fiber tracts, leading to a
264 higher specificity in detecting structural changes ³⁶.

265 Deviations in scalar DWI measures in the current study relative to previous studies could also
266 be due to ongoing white matter maturation processes in our adolescent EOP sample. In
267 healthy individuals, age-related increases in FA during childhood, adolescence and early
268 adulthood have been consistently reported ³⁷⁻⁴⁰. This increase in FA seems primarily driven by
269 a reduction in RD, while AD remains fairly stable or decreases slightly ^{41,42}. Findings for AD
270 changes during the transition to adulthood are less consistent ³⁷⁻⁴⁰. Thus, the AD difference
271 found in the current study could also be attributed to developmental processes, which may
272 fade as adolescents mature into adulthood.

273 However, it should be noted that the neurodevelopmental trajectories of white matter structure
274 relative to disease progression in EOP patients are unclear. So far, three different studies
275 yielded inconclusive results, postulating either diverging ¹³, converging ⁴³, or parallel ⁴⁴
276 trajectories relative to healthy controls. In the current study, we did not find any predictive value
277 of duration of illness for regional FA. This is in line with previous findings from Kumra and
278 colleagues, who speculated that the decrease in FA in EOP patients compared to healthy
279 controls reflects developmental abnormalities rather than secondary effects of the disease
280 progression ¹³. In addition, Epstein and Kumra found lower FA in the inferior longitudinal
281 fasciculus, IFOF and corticospinal tract, but no significant group differences in longitudinal
282 changes in FA ⁴⁴. Thus, the observed changes in the current study might persist but do not

283 affect the overall white matter maturation trajectories. However, the cross-sectional nature of
284 the current study precludes the assessment of developmental effects over time.

285 The results of the current study should be considered in the context of several limitations.
286 Unmedicated EOP patients were significantly younger than those receiving medication.
287 Although the analysis was corrected for age, we cannot exclude that the age of the patients
288 contributes to the observed antipsychotic-medication related changes in white matter structure.
289 It is possible that time-of-measurement effects, with older patients having higher FA values
290 than younger patients due to more advanced white matter maturation, could confound our
291 results. However, while we acknowledge this possibility, we consider this unlikely to be the
292 driving mechanism for the following reason: we would expect differences in FA values in other
293 regions showing a similar maturation trajectory, such as the SLF ⁴¹, if our results were mainly
294 driven by age differences. This was not the case, as we found no significant difference in mean
295 FA values of the SLF between medicated and unmedicated patients ($t = -0.56934$, $p\text{-value} =$
296 0.576). We further stress that we did not find any associations between regional FA variation
297 and clinical measures such a PANSS scores, which is likely due to the relatively small sample
298 size.

299 In summary, the present study is the first to link antipsychotic medication status to altered
300 regional FA in the left ACR in patients with EOP. Understanding the significance of white matter
301 abnormalities in the left ACR in adolescents with EOP and the putatively remediating effect of
302 antipsychotic medication, may help to phenotype the disease and to develop new
303 pharmacological regimes to subsequently improve functional outcome. Assuming that
304 antipsychotic medication reverses the hypothesized myelin dysfunction in psychosis, early
305 interventions with antipsychotic medication, already in individuals at risk of developing
306 psychosis, could provide the opportunity to normalize white matter maturation. Although
307 exciting, further work is needed to draw firm conclusions about the beneficial effects of
308 antipsychotic medication early in the disease process. Building on our first results, longitudinal
309 studies with larger samples sizes using high resolution DWI in combination with clinical, genetic
310 and neurocognitive measures are warranted to delineate heritability, affected brain regions,
311 antipsychotic medication effects, and directions of FA changes over time.

312 **Methods**

313 ***Participants***

314 The study sample was drawn from the ongoing longitudinal Youth-Thematic-Organized-
315 Psychosis (Youth-TOP) research study, which is a subdivision of the TOP research
316 group/NORMENT and KG Jebsen center of psychosis research in Oslo, Norway. EOP patients,
317 aged between 12-18 years, were recruited from in- and outpatient clinics in the Oslo region.
318 Healthy controls were randomly selected from the Norwegian National Registry in the same
319 catchment area. All participants and their respective parents/guardians provided written
320 informed consent. The study was approved by the Regional Committee for Medical Research
321 Ethics (REK-Sør) and the Norwegian Data Inspectorate and was conducted in accordance
322 with the Declaration of Helsinki.

323 For study inclusion, participants were required to have an intelligence quotient (IQ) > 70, a
324 good command of the Norwegian language, no previous moderate to severe head injuries, no
325 diagnosis of substance-induced psychotic disorder, and no organic brain disease. IQ was
326 measured by the Wechsler Abbreviated Scale of Intelligence⁴⁵. Diagnosis was established
327 according to the Diagnostic and Statistical Manual of Mental Disorder- IV criteria using the
328 Norwegian version of the Kiddie-Schedule for Affective Disorders and Schizophrenia for
329 School Aged Children (6-18 years): Present and Lifetime Version (K-SADS-PL⁴⁶). The clinical
330 characterization was conducted by trained psychologists or psychiatrists.

331 A total of 67 participants (27 patients/40 controls) satisfied the above-mentioned criteria and
332 underwent MRI examination. All MRI scans were visually inspected by a trained
333 neuroradiologist to rule out any pathological changes. Out of the initial sample, seven control
334 participants and five patients were excluded due to (i) clinical/radiological reasons (five
335 patients/ three controls), or (ii) strong motion artefacts in the diffusion imaging data (four
336 controls), resulting in a final sample of 55 participants (22 patients/ 33 controls) being entered
337 in the statistical analysis.

338 Sample demographics and clinical characteristics separated by antipsychotic medication
339 status of EOP patients are reported in Table 1 and Table 2, respectively.

340 ***Clinical measures***

341 Presence and severity of psychopathological symptoms of EOP patients were assessed using
342 the Positive and Negative Syndrome Scale (PANSS⁴⁷). Children Global Assessment Scale
343 (CGAS⁴⁸) and Mood and Feelings Questionnaire (MFQ, long version⁴⁹) were evaluated in all
344 participants to measure general functioning level and to screen for depressive symptoms,

345 respectively. Recreational drug use was assessed within the structured K-SADS interview and
346 scored with 0 or 1 for absent or present. For EOP patients, current and lifetime cumulative use
347 of medication was recorded and converted into chlorpromazine equivalents (CPZ), using
348 formulas published elsewhere⁵⁰. While 11 EOP patients were off any antipsychotic medication
349 at scan, yielding a lack of current CPZ values, 3 patients had received pharmacological
350 treatment prior to inclusion, resulting in a low cumulative CPZ dosage for this subgroup (see
351 Table 2).

352 ***MRI data acquisition***

353 MR images were acquired on a 3-Tesla General Electric Signa HDxt scanner equipped with
354 an 8-channel head coil at the Oslo University Hospital, Norway. The diffusion imaging data
355 was acquired using a 2D spin-echo whole-brain echo-planar imaging sequence with the
356 following parameters: slice thickness = 2.5 mm, repetition time = 15 s, echo time = 85 ms, flip
357 angle = 90°, acquisition matrix = 96 x 96, in-plane resolution = 1.875 x 1.875 mm. A total of 32
358 volumes with different gradient directions ($b = 1000 \text{ s/mm}^2$), including two b_0 -volumes with
359 reversed phase-encode (blip up/down), were acquired.

360 ***Diffusion data analysis***

361 Diffusion data were analyzed with FSL version 5.0.9 using the FMRIB's software library
362 (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>). Before creating voxel wise maps of diffusion parameters,
363 the following steps of the standard processing pipeline were used: (i) *topup* to correct for
364 susceptibility-induced distortions^{51,52}, (ii) *eddy* current correction to correct for gradient-coil
365 distortions and head motion⁵³, (iii) removal of non-brain tissue using the Brain Extraction Tool
366 (*bet*)⁵⁴, and (iv) local fitting of the diffusion tensor at each voxel using *dtifit* (FMRIB's Diffusion
367 Toolbox (FDT)⁵⁵). *Dtfit* yielded in voxel wise participant-specific maps of FA, mean diffusion
368 (MD), and axial diffusivity (AD, derived from eigenvector λ_1). Based on the outputted
369 eigenvectors λ_2 and λ_3 , radial diffusivity (RD) was computed $((\lambda_2 + \lambda_3)/2)$. Next, voxel wise
370 statistical analysis of the FA data was carried out using TBSS⁵⁶. First, all FA images were
371 nonlinearly aligned to the most representative FA image out of all images and transformed into
372 $1 \times 1 \times 1 \text{ mm}^3$ MNI152 standard space by means of affine registration. Secondly, TBSS projects
373 all participant's FA data onto a mean FA tract skeleton (threshold FA > 0.25), before applying
374 voxel wise cross-participant statistics. After TBSS for FA was completed, results were used to
375 generate skeletonized RD and AD data for additional voxel-wise group comparisons using the
376 TBSS non-FA pipeline.

377

378 **Statistical analyses**

379 For contrasting case-control differences, we run voxel-wise statistics, co-varied for age and
380 gender, using a nonparametric permutation-based approach (*Randomise*, implemented in FSL,
381 5000 permutations). All variables were demeaned. The statistical threshold was set at $p \leq 0.01$,
382 after family-wise error correction for multiple comparisons using threshold-free cluster
383 enhancement. We chose a highly conservative threshold for FA to minimize type I errors and
384 to better account for the exploratory nature of the study concerning the impact of antipsychotic
385 medication status. For RD and AD, the same statistical model was used.

386 Regions identified with TBSS (FA) and TBSS non-FA (RD or AD) were subsequently used as
387 masks to extract mean FA, RD and AD values for plotting and further analysis. We refrained
388 from using MD values, as a measure of overall diffusivity within a voxel, in further analysis due
389 to its lack of specificity⁴. As scalar diffusion measures largely vary in their value ranges,
390 extracted mean values were z-standardized for plotting purposes using the following formula:
391 $z = (\text{participant's value} - \text{group mean}) / \text{standard deviation}$.

392 A linear regression model was performed to examine whether patients' mean values of
393 significant TBSS and TBSS non-FA clusters were associated with duration of illness and
394 antipsychotic medication status as categorical variable (coded as yes (1)/no (0)). The effect
395 size was reported as Cohen's d ⁵⁷.

396 If there is an association between patients' regional mean values and antipsychotic medication,
397 follow-up correlation analysis with current and cumulative CPZ were performed using
398 Spearman's rank correlation ρ for non-normal data.

399 Further analysis of regional mean values and its association with clinical measures (PANSS,
400 CGAS, MFQ) were performed using Pearson's product moment correlation coefficient.

401 Statistical tests were conducted in R, version 3.5.2 (www.r-project.org).

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586 **Author Contributions**

587 CB undertook the processing of the imaging data, the statistical analysis, the literature search,
588 interpreted the results and wrote the first draft of the manuscript. TPG helped with the
589 processing of the imaging data. VL was significantly involved in the participant inclusion and
590 data acquisition for Youth-TOP and calculated current and cumulative chlorpromazine
591 equivalents. IA designed the ongoing longitudinal Youth-TOP research study the data is drawn
592 from. IA, AMM and OAA obtained funding and contributed to the data acquisition. All authors
593 contributed to the critical revision of the manuscript and approved the final draft for submission.

594 **Additional Information**

595 **Competing interests**

596 The authors declare no competing interests.

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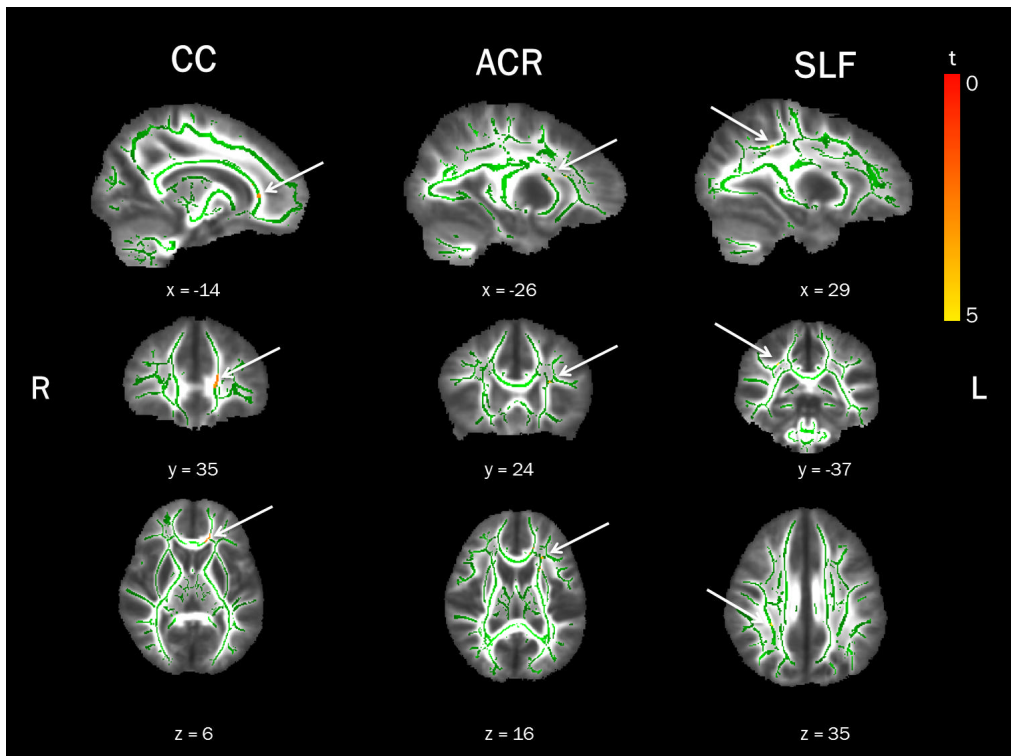
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605 **Figures**



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607 **Figure 1| Lower fractional anisotropy (FA) in early onset psychosis (EOP) patients in**
608 **comparison to healthy controls.** Displayed are significant FWE-corrected TBSS results (red-
609 yellow, $p \leq 0.01$), contrasting EOP patients against healthy controls, overlaid on the study-specific mean
610 FA skeleton in green and the mean FA image. Results shown underwent threshold-free cluster
611 enhancement and are corrected for age and sex. CC = corpus callosum, ACR = anterior corona radiata,
612 SLF = superior longitudinal fasciculus, R = right, L = left.

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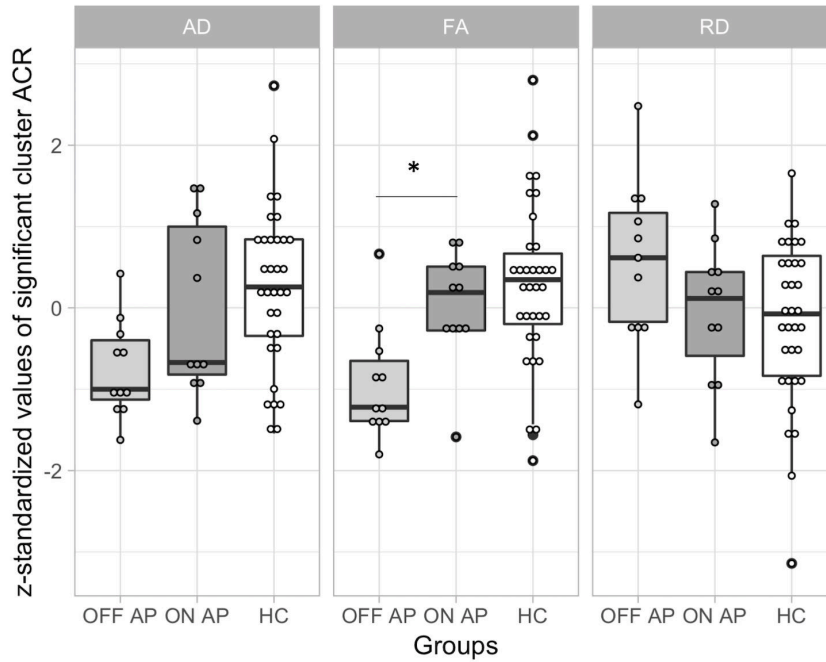
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620 **Figure 2| Extracted scalar diffusion values of the left anterior corona radiata (ACR)**
621 **cluster stratified by antipsychotic use, in comparison to the healthy controls (HC).** Data
622 is z-standardized and presented as boxplots for the different scalar diffusion measures overlaid with raw
623 data points. HC are depicted in white, EOP patients on antipsychotic medication in dark grey and EOP
624 patients off antipsychotic medication in light grey. EOP = Early onset psychosis, AP = Antipsychotic use
625 (on = yes, off = no), AD = axial diffusion, FA = fractional anisotropy, RD = radial diffusion. Significant
626 differences in scalar measures between patient subgroups, based on linear regression models, are
627 indicated with a star.

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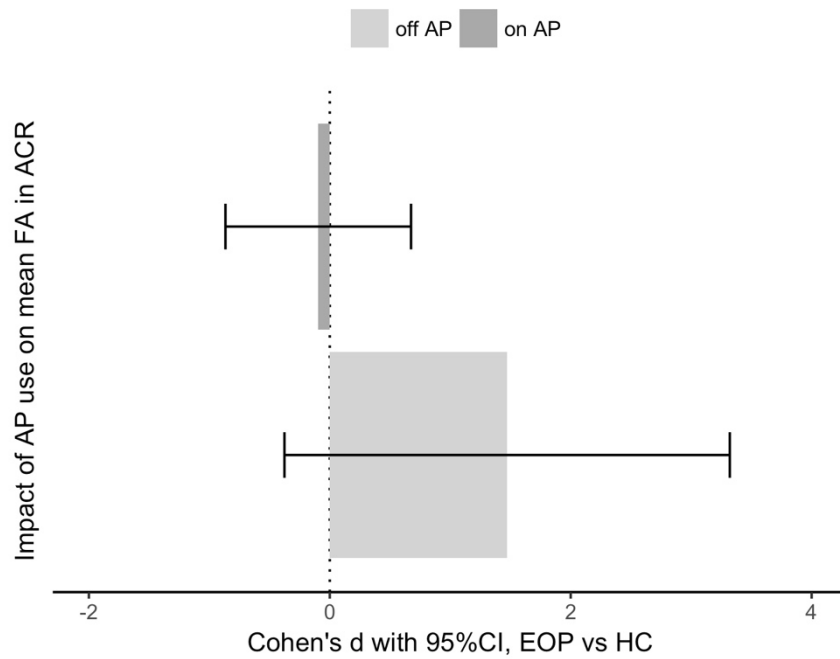
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635 **Figure 3| Effect size of antipsychotic medication effect on fractional anisotropy (FA) in**
636 **left anterior corona radiata (ACR).** Effect size is presented as Cohen's d with 95% confidence
637 interval (CI) to show the standardized difference of antipsychotic medication status (AP) of early onset
638 psychosis (EOP) patients relative to healthy controls (HC, N = 28). EOP patients on AP (N = 8) are
639 depicted in dark grey and EOP patients off AP (N = 11) are depicted in light grey. Results are controlled
640 for age, sex and BMI.

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652 **Tables**

653 **Table 1| General sample characteristics.**

| | <i>EOP patients overall</i> <i>N = 22</i> | <i>Healthy controls</i> <i>N = 33</i> | <i>Statistics</i> <i>group-level</i> |
|-------------------------------|--|--|---|
| Sex (m/f) | 7/15 | 13/20 | $X^2 = 0.33, p = 0.775$ |
| Age at MRI (y) | 16.69 ± 1.13 | 16.08 ± 1.43 | $t = 1.76, p = 0.085$ |
| Range | 14.53 – 18.25 | 12.67 – 18.15 | |
| Handedness (r/l) | 18/2 | 30/2 | FET, $p = 0.634$ |
| Missing N (%) | 2 (9.1) | 1 (3) | |
| Parental Education (y) | | | |
| Mother | 15.05 ± 1.94 | 16.13 ± 2.09 | $t = -1.94, p = 0.058$ |
| Range | 11 – 19 | 12 – 22 | |
| Missing N (%) | 0 | 2 (6.1) | |
| Father | 14.67 ± 2.87 | 15.57 ± 2.39 | $t = -1.18, p = 0.245$ |
| Range | 10 – 23 | 11 – 20 | |
| Missing N (%) | 1 (4.5) | 3 (9.1) | |
| IQ | 102.74 ± 11.82 | 101.81 ± 11.32 | $t = 0.27, p = 0.785$ |
| Range | 83 – 132 | 70 – 116 | |
| Missing N (%) | 3 (13.63) | 1 (3) | |
| CGAS | 44.95 ± 8.57 | 89.15 ± 6.56 | MWU test, $p < 0.001$ |
| Range | 32 – 59 | 75 – 98 | |
| MFQ | 29.05 ± 12.79 | 6.19 ± 6.5 | MWU test, $p < 0.001$ |
| Range | 5 – 52 | 0 – 31 | |
| Missing N (%) | 1 (4.5) | 1 (3) | |
| BMI (kg/m²) | 21.65 ± 5.6 | 20.81 ± 2.6 | MWU test, $p = 0.704$ |
| Range | 15.4 ± 35.4 | 16.7 ± 26.0 | |
| Missing N (%) | 3 (13.63) | 5 (15.15) | |
| Cannabis (yes/no) | 7/15 | 1/32 | FET, $p = 0.005$ |

654 All values in mean ± standard deviation, N = Number of participants, m = male, f = female, y = years, r
655 = right, l = left, IQ = Intelligence Quotient, BMI = Body Mass Index, CGAS = Children's Global
656 Assessment Scale, MFQ = Mood and Feelings Questionnaire, MWU = Mann-Whitney-U, FET = Fisher's
657 Exact Test

658 **Table 2| Patient clinical characteristics stratified by antipsychotic medication status**

| | <i>EOP patients</i> <i>Off AP at scan</i> <i>N = 11</i> | <i>EOP patients</i> <i>On AP at scan</i> <i>N = 11</i> | <i>Statistics</i> <i>patient-level</i> |
|-------------------------------|---|--|---|
| Sex (m/f) | 5/6 | 2/9 | FET, $p = 0.361$ |
| Age Scan (y) | 15.94 ± 1.49 | 17.44 ± 0.65 | $t = -4.19, p = 0.0006$ |
| Range | 14.53 – 17.25 | 16.53 – 18.25 | |
| BMI (kg/m²) | 20.53 ± 4.32 | 23.2 ± 7.02 | MWU test, $p = 0.492$ |
| Range | 15.4 – 28.7 | 16.3 – 35.4 | |
| Missing N (%) | 0 | 3 (27.3) | |
| CGAS | 46 ± 8 | 43.91 ± 9.38 | $t = 0.56, p = 0.580$ |
| Range | 34 – 59 | 32 – 58 | |
| MFQ | 30.82 ± 12.6 | 27.1 ± 13.39 | $t = 0.65, p = 0.521$ |
| Range | 5 – 52 | 8 – 49 | |
| Missing N (%) | 0 | 1 (9.1) | |
| PANSS | | | |
| <i>positive</i> | 19.09 ± 3.83 | 17.18 ± 3.84 | $t = 1.17, p = 0.257$ |
| Range | 12 – 25 | 13 – 26 | |
| <i>negative</i> | 22.09 ± 7.13 | 18.27 ± 6.96 | $t = 1.27, p = 0.218$ |
| Range | 9 – 32 | 7 – 32 | |
| <i>general</i> | 38.73 ± 8.44 | 36.27 ± 7.89 | $t = 0.70, p = 0.489$ |
| Range | 28 – 54 | 24 – 52 | |
| Age of Onset (y) | 14.39 ± 1.92 | 14.83 ± 2.07 | $t = -0.51, p = 0.614$ |
| Range | 10 – 16 | 12 – 17.6 | |
| DUP (w) | 67.36 ± 68.33 | 24.73 ± 35.58 | MWU test, $p = 0.003$ |
| Range | 14 – 227 | 3 – 125 | |
| DUI (y) | 1.54 ± 1.44 | 2.61 ± 2.17 | MWU test, $p = 0.401$ |
| Range | 0.47 – 4.53 | 0.33 – 5.97 | |
| Diagnosis | | | |
| SCZ | 7 | 7 | |
| SCA | 1 | 0 | |
| NOS | 3 | 4 | |
| Antipsychotics | | | |
| Aripiprazole | | 5 | |
| Risperidone | | 3 | |
| Quetiapine | | 3 | |
| CPZ | | | |
| <i>current</i> | | 272.3 ± 140.83 | |
| Range | | 151.52 – 559.44 | |

| | | | |
|------------------------------|-------------|--------------|------------|
| <i>cumulative</i> | 0.08 ± 0.28 | 21.6 ± 19.13 | |
| (AP-naïve, N = 9) | | | |
| Range | 0 – 0.92 | 1.69 – 59.28 | |
| Cannabis use (yes/no) | 3/8 | 4/7 | FET, p = 1 |

659 *All values in mean ± standard deviation, AP = antipsychotics, N = number of participants, m = male, f
660 = female, y = years, r = right, l = left, IQ = Intelligence Quotient, BMI = Body Mass Index, CGAS =
661 Children’s Global Assessment Scale, MFQ = Mood and Feelings Questionnaire, PANSS = Positive and
662 Negative Symptom Scale, DUP = Duration of Untreated Psychosis, DUI = Duration of illness, SCZ =
663 schizophrenia, SCA = schizoaffective, NOS = psychosis, not other specified, CPZ = chlorpromazine
664 equivalent, MWU = Mann-Whitney-U, FET = Fisher’s Exact Test.

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666 **Table 3| White matter cluster of reduced fractional anisotropy in early onset psychosis**
667 **patients relative to healthy controls.**

| Cluster | Region* ¹ | Side | Voxels | MNI coordinates in mm | | | t-values |
|---------|---|------|--------|-----------------------|-----|----|----------|
| | | | | X | Y | Z | |
| 4 | Genu of corpus callosum | L | 150 | -14 | 35 | 6 | 3.35 |
| 3 | Anterior corona radiata* ² | L | 46 | -26 | 13 | 14 | 3.69 |
| 2 | Superior longitudinal fasciculus | R | 12 | 29 | -37 | 35 | 4.81 |
| 1 | Anterior corona radiata (16% Inferior fronto-occipital fasciculus) * ³ | L | 9 | -26 | 24 | 16 | 4.05 |

668 *¹ Johns Hopkins University International Consortium for Brain Mapping (JHU ICBM)-DTI-81 white
669 matter atlas and JHU white matter tractography atlas (in brackets) were utilized to label significant
670 clusters with specific tract names

671 *² 6% uncinate fasciculus/ 5% inferior fronto-occipital fasciculus according to JHU White-Matter
672 Tractography Atlas

673 *³ 11% anterior thalamic radiation, 8% uncinate fasciculus according to JHU White-Matter Tractography
674 Atlas