**Supplemental Method section** (based on Domen et al, *Schizophrenia Research,* 2013 and Domen et al, *Schizophrenia Bulletin*, 2017)

Participants

Subjects were recruited in the context of a multicentre longitudinal (baseline, +3 and +6 years) study (Genetic Risk and Outcome of Psychosis, G.R.O.U.P.) in the Netherlands. The main object was to investigate gene-environment vulnerability and resilience in patients with a psychotic disorder, their unaffected family members and healthy controls (Korver *et al.* 2012).

Patients with psychotic disorder (n=85) were identified through clinicians at mental health in- and outpatient services in selected representative geographical areas in the Netherlands and Belgium. Siblings (n=93) were contacted through participating patients and controls (n=80) were recruited through mailings and advertisements in local newspapers of the same geographical area.

At follow-up, approximately three years later (mean: 3.3 years), DTI scans were acquired from a sample of 180 participants (61 patients with a psychotic disorder, 61 siblings without a psychotic disorder and 58 healthy controls; i.e. attrition was 40%). For 159 of these 180 participants (55 patients with a psychotic disorder, 55 siblings without a psychotic disorder and 49 healthy controls), a valid pair of DTI scans was available for longitudinal analysis. The sample included 129 families of which 16 families contributed one patient and one healthy sibling and 1 family contributed one patient and two healthy siblings. 6 families contributed two healthy siblings, 1 family contributed three healthy siblings and 4 families contributed two healthy controls. In addition, 38 families contributed a single patient, 22 families contributed a single sibling, and 41 families contributed a single control.

Inclusion criteria were: age range 16-50 years, illness duration <10 years, a diagnosis of non-affective psychotic disorder and sufficient command of the Dutch language.

All participants were screened before MRI acquisition for the following exclusion criteria: brain injury with unconsciousness greater than 1 hour, meningitis or other neurological diseases with possible impact on brain structure or function, cardiac arrhythmia requiring medical treatment and severe claustrophobia. In addition, subjects with metal corpora aliena were excluded, as were women with intrauterine device status and (suspected) pregnancy.

*Psychopathology*

Psychopathology was assessed in all three groups, measured with the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen *et al.* 1992), wherein the diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria (APA 2000). At baseline and follow-up, none of the siblings and the controls had a history of a psychiatric disorder, despite a proportion (follow-up: 15 siblings, 11 controls) with a history of major depressive disorder (Table 1).

*AP medication*

Antipsychotic (AP) medication use at baseline was determined by patient report and verified with the treating consultant psychiatrist. Best estimate lifetime (cumulative) AP use was determined by multiplying the number of days of AP use with the corresponding haloperidol equivalents and summing these scores for all periods of AP use (including the exposure period between baseline assessment for the G.R.O.U.P. study and the moment of baseline MRI scanning), using the converting formulas for AP dose equivalents described by Andreasen and colleagues (Andreasen *et al.* 2010). The same procedure was used for calculating cumulative AP exposure during the 3-year follow-up period.

Diffusion tensor imaging analysis

First, standard Siemens DICOM files were transformed into compressed NIFTI format using a custom built in-house software named GIANT (General Image ANalysis Tools developed by Ed Gronenschild). Raw data were corrected for head movement and eddy currents invoked during scanning. The B0 volume was skull-stripped using FSL's Brain Extraction Tool (Smith 2002) and this served as a brain mask for all B volumes.

The next step was fitting a diffusion tensor model at each voxel using data output from the brain extraction, diffusion weighted data and gradient directions following a general linear model (FreeSurfer v4.5.0, http://www.freesurfer.net). After tensor fitting (using the DT-Recon script) the process continued working on FA volumes, eroding them slightly. Nonlinear registration aligned each FA volume to 1 x 1 x 1 mm standard FMRIB58\_FA space. The standard FMRIB58\_FA contains a template derived from high-resolution images of 58 participants in a well-aligned population (both males and females ranging between 20 and 50 years of age) (Smith *et al.* 2006).

For the current study, three mean FA skeletons were created; for the cross-sectional analysis at baseline (n=258: controls, siblings, patients) and at follow-up (n=180) and, for the longitudinal analysis, one based on six groups (3 groups × 2 time-points). The mean FA skeleton follows the major WM tracts in each individual participant (normalized in MNI152 space) and provides a way to compare between (groups of) participants. The FA threshold was set, using visual inspection of the FA skeleton, at a level of 0.25, to include major WM tracts whilst removing small peripheral tracts that would cause excess inter-participant variability. In addition, this threshold setting avoided inclusion of regions that are likely to be composed of multiple tissue types or fiber orientations. In the final step, a binary skeleton mask of the individual participants was created and used to extract FA values of most large WM tracts (n=38) in order to create a whole-brain mean FA for the subsequent statistical analyses. The Johns Hopkins University International Consortium for Brain Mapping (JHU ICBM)-DTI-81 white-matter atlas labels (Mori *et al.* 2008) and the JHU white-matter tractography atlas (Hua *et al.* 2008) were used to identify and assign a specific tract name to as much voxels as possible.

Statistical analyses

To examine cross-sectional associations between the environmental exposures (lifetime and last year cannabis use, childhood trauma) and whole-brain mean FA at baseline (n=258) and at follow-up (n=180), the data set was transformed from a wide to a long format, resulting in a hierarchically structured data set, based on 38 regional mean FA measures (Level 1) nested in subjects (Level 2) who were part of the same families (Level 3).

**References**

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