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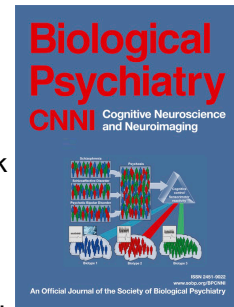
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Association of whole-genome and NETRIN1 signaling pathway-derived polygenic risk scores for Major Depressive Disorder and white matter microstructure in UK Biobank

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Abstract

Background: Major Depressive Disorder (MDD) is a clinically heterogeneous psychiatric disorder with a polygenic architecture. Genome-wide association studies have identified a number of risk-associated variants across the genome, and growing evidence of NETRIN1 pathway involvement. Stratifying disease risk by genetic variation within the NETRIN1 pathway may provide important routes for identification of disease mechanisms by focusing on a specific process excluding heterogeneous risk-associated variation in other pathways. Here, we sought to investigate whether MDD polygenic risk scores derived from the NETRIN1 signaling pathway (NETRIN1-PRS) and the whole genome excluding NETRIN1 pathway genes (genomic-PRS) were associated with white matter microstructure.

Methods: We used two diffusion tensor imaging measures, fractional anisotropy (FA) and mean diffusivity (MD), in the most up-to-date UK Biobank neuroimaging data release (FA: N = 6,401; MD: N = 6,390).

Results: We found significantly lower FA in the superior longitudinal fasciculus ($\beta = -0.035$, $p_{\text{corrected}} = 0.029$) and significantly higher MD in a global measure of thalamic radiations ($\beta = 0.029$, $p_{\text{corrected}} = 0.021$), as well as higher MD in the superior ($\beta = 0.034$, $p_{\text{corrected}} = 0.039$) and inferior ($\beta = 0.029$, $p_{\text{corrected}} = 0.043$) longitudinal fasciculus and in the anterior ($\beta = 0.025$, $p_{\text{corrected}} = 0.046$) and superior ($\beta = 0.027$, $p_{\text{corrected}} = 0.043$) thalamic radiation associated with NETRIN1-PRS. Genomic-PRS was also associated with lower FA and higher MD in several tracts.

Conclusions: Our findings indicate that variation in the NETRIN1 signaling pathway may confer risk for MDD through effects on a number of white matter tracts.

Introduction

Major Depressive Disorder (MDD) is a common and frequently disabling psychiatric disorder and a leading cause of disability worldwide (1). MDD is known to result from a complex combination of environmental and genetic factors (2; 3), with a moderate heritability of approximately 37% (4; 5; 6).

Genome-wide association studies (GWAS) suggest that at least part of MDD's heritability is due to the cumulative effect of alleles of small effect size (7; 8) and have identified a number of risk-associated genetic variants across the genome (6; 7; 9; 10; 11). Significant findings for GWAS analyses can also be annotated to specific biological pathways, revealing underlying cellular and molecular mechanisms.

Following several GWAS, the Psychiatric Genomics Consortium (PGC) have identified an aggregation of variants in several specific biological pathways (12; 13). In MDD, Zeng et al. (2017) (14) combined pathway and regional heritability analysis in two independent samples and reported that the NETRIN1 signaling pathway was involved in the genetic aetiology of MDD. Moreover, polygenic risk scores (PRS) calculated for this pathway alone more accurately predicted MDD in one of the cohorts compared to PRS calculated for the whole genome. Genetic variation within the NETRIN1 signaling pathway may therefore capture more aetiologically circumscribed liability for MDD that is less susceptible to heterogeneous influences from other biological pathways.

Animal studies have previously indicated that NETRIN1, by binding to and activating NETRIN1 receptors such as 'Deleted in Colorectal Cancer' (DCC), plays an important role in commissural and cortical axon guidance (15). More recently, DCC was identified as playing a crucial role in thalamic axonal growth, confirming that interaction of NETRIN1 with DCC

leads to successful axon growth during central nervous system development (16). GWAS of other traits related to MDD have also shown an aggregation of variants in the NETRIN1 pathway (17; 18).

Previous studies have attempted to investigate psychiatric disorders by examining relevant quantitative traits such as brain structure or function (19). Differences in white matter (WM) integrity as measured by diffusion tensor imaging (DTI) have been found between MDD patients and healthy participants in numerous studies, although findings have been widely inconsistent (20; 21; 22). For example, Shen et al. (2017) (20) found significantly lower global white matter integrity in association fibres and thalamic radiations, as measured by fractional anisotropy (FA), in MDD patients compared to healthy individuals. More specifically, they also found lower FA in the left superior longitudinal fasciculus, superior thalamic radiations and forceps major tracts in MDD patients. Lower WM integrity as measured by FA has also been found in adolescents with MDD as compared to age-matched healthy individuals (21; 22).

It has previously been shown that the NETRIN1 signaling pathway is associated with MDD and white matter microstructure (14). Therefore, in the current study, we sought to investigate the association between MDD risk-associated variants in the NETRIN1 signaling pathway and white matter integrity. We first created polygenic risk scores for pathway SNPs (NETRIN1-PRS) and SNPs excluded from the pathway (genomic-PRS). We then tested their association with WM integrity as measured by FA and mean diffusivity (MD). We used the most up-to-date genetic and imaging data available (N after exclusion steps: FA = 6,401; MD = 6,390) from UK Biobank (UKB). We hypothesized that NETRIN1-PRS would be

significantly associated with WM integrity, after adjustment for genomic-PRS, indicating a potential role of the pathway in MDD pathophysiology.

ACCEPTED MANUSCRIPT

Methods and Materials

UK Biobank

The UKB study consists of 502,617 community-dwelling individuals who were recruited between 2006 and 2010 in the United Kingdom (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200>). UKB received ethical approval from the Research Ethics Committee (reference: 11/NW/0382). This study has been approved by the UKB Access Committee (Project #4844). Written informed consent was obtained from all participants.

Study population

In the most recent UKB imaging data release, 8,839 individuals (N female = 4,639; N male = 4,200; mean age: 62.54 +/- 7.42 years; age range: 45.17 – 79.33) completed DTI assessment, and a quality check by UKB. In addition to this, for the current study, individuals were excluded if they participated in studies from the PGC MDD GWAS (24) or Generation Scotland (Scottish Family Health Study), or if they happened to be related, as the PGC MDD GWAS dataset was used in order to calculate PRS. Moreover, individuals whose FA and MD values were greater than three standard deviations above/below the mean were not included in the study (Supplementary Material, tables S4 and S5). This resulted in 6,401 individuals with FA values (N female = 3,334; N male = 3,067; mean age: 62.60 +/- 7.37; age range: 45.92 – 78.42; N_{control}: 3,736; N_{case}: 2,512) and 6,390 individuals with MD values (N female = 3,327; N male = 3,063; mean age: 62.58 +/- 7.36; age range: 45.92 – 78.42; N_{control}: 3,729; N_{case}: 2,508), excluding 19 and 30 individuals with FA and MD values from a total of 6,420, respectively. Details of data exclusion as well as participant information for the full dataset (N = 6,420) are shown in the Supplementary Material (tables S1 and S2).

SNP annotation

Genic SNPs found in the NETRIN1 signaling pathway as taken from Zeng et al.'s (2017) study (14) (N genes = 43; gene list is presented in the Supplementary Material, table S3) and genic SNPs excluded from the pathway were annotated using the program ANNOVAR. ANNOVAR is a biostatistical tool used to annotate genetic variants to functional genomic regions (23). In the current study, we performed a gene-based annotation for SNPs used in the largest available GWAS of MDD (N=461,134, of which 130,664 were MDD cases), carried out by the Psychiatric Genomics Consortium (24), which includes summary statistics from the personal genetics company 23andMe, Inc. (10). We defined gene boundaries as an extended region of 20 kb from transcription start sites and transcription end sites. After SNPs were annotated to genes, they were further mapped to the NETRIN1 signalling pathway. All protein-coding genes within this file were annotated in reference to hg 19. Intergenic SNPs were not included in the annotated files. The resulting output file included: function of each SNP, gene name, chromosome number, start position, end position, reference and alternative alleles, odds ratio, standard error and p-value for each variant.

Following functional annotation, a file containing the 43 gene names included in the NETRIN1 signaling pathway was used as an input in order to extract gene-based SNPs located in the pathway. For the genomic-PRS, all gene-based SNPs excluding those implicated in the NETRIN1 signaling pathway were extracted. The two files were then used as input for creation of PRS.

Genotyping and PRS profiling

A total of 488,363 UKB blood samples (N female = 264,857; N male = 223,506; <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=22001>), were genotyped using two different arrays: UK BiLEVE array (N = 49,949)

(<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=149600>) and UK Biobank Axiom array (N = 438,417) (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=149601>). Details of genotyping and quality control are described in more detail by Hagenaars et al. (2016) (25) and Bycroft et al. (2017) (26).

Using the largest available GWAS of MDD, PRS for each individual were computed using PRSice (27), at five p-value thresholds (0.01, 0.05, 0.1, 0.5, 1) by adding the number of risk alleles and weighting them by the strength of association with MDD. PRS were created both from SNPs annotated to the NETRIN1 signalling pathway and from SNPs from the rest of the genome, thus resulting in separate PRS lists. PRS were created both with and without clump-based pruning of SNPs in linkage disequilibrium ($r^2 = 0.25$, 250km window). The primary analysis reported in this manuscript concerns unpruned SNPs, owing to the potential of causal variants within the NETRIN1 pathway to be in LD with other variants, and uses SNPs which met a significance level of $p = 0.5$, in line with previous studies (28; 29). Secondary analyses with other PRS p-value thresholds, as well as with LD pruned SNPs, are presented in the Supplementary Material (Tables S6 – S21).

MRI acquisition

In the present study, imaging-derived phenotypes (IDPs) produced by UKB were used. MRI acquisition and pre-processing procedures for FA and MD values of white matter tracts were performed by UKB using standardised protocols (https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf). Briefly, images were collected on a single Siemens Skyra 3.0 T scanner with a standard Siemens 32-channel head coil and were pre-processed using FSL packages; parcellation of white matter tracts was conducted using AutoPtx (30).

Summary data were composed of tract-averaged FA and MD values for 15 major white

matter tracts, of which 12 are bilateral and three are unilateral. The white matter tracts were also categorised into three separate subsets, as follows: association fibres: inferior fronto-occipital fasciculus, uncinate fasciculus, cingulum bundle (gyrus and parahippocampal), superior and inferior longitudinal fasciculus; thalamic radiation fibres: anterior, superior and posterior thalamic radiations; projection fibres: forceps major and minor, corticospinal tract, acoustic radiation, medial lemniscus and middle cerebellar peduncle. Global measures of FA and MD are referred to as general factors of FA and MD (gFA and gMD, respectively).

Exclusion criteria comprised removal of scans with severe normalisation problems by UKB. Moreover, individuals whose FA and MD values were higher than three standard deviations from the sample mean were also excluded. Results for the full dataset with outliers included are also presented in the Supplementary Material (tables S1 and S2). Lastly, due to the fact that the position of the head and radio-frequency coil in the scanner may affect data quality as well as IDPs, three scanner brain position variables which may be used as confounding variables in subsequent analyses were generated by UKB: lateral brain position – X (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=25756>), transverse brain position – Y (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=25757>) and longitudinal brain position – Z (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=25758>). The three variables were included as covariates in the statistical analysis described below.

Statistical methods

All analyses were conducted using R (version 3.2.3) in a Linux environment. In order to test the association between the NETRIN1 signaling pathway- and genomic pathway-derived unpruned PRS lists, we used repeated measures linear mixed-effects models (function “lme” in package “nlme”) for 12 bilateral brain regions, correcting for hemisphere, with age, age², sex, fifteen genetic principal components, three MRI head position coordinates and genotype

array set as covariates. For unilateral tracts, global measures of FA and MD, and tract categories, we used a general linear model (function “lm”), using the same covariates as above, and without hemisphere included as a separate term in the model. All models included both the genomic-PRS and the NETRIN1-PRS as predictor variables.

First, we tested the association between unpruned PRS (both NETRIN1-PRS and genomic-PRS) and global white matter integrity. We applied principal component analysis (PCA) on the 27 white matter tracts (12 tracts in both the right and left hemisphere and three unilateral tracts) in order to extract a latent measure. Scores of the first unrotated component of FA and MD (variance explained = 37.52% for FA and 38.83% for MD) were extracted and set as the dependent variable in a general linear model in order to test association with both NETRIN1-PRS and genomic-PRS.

We then examined the three categories of white matter tracts by applying PCA on the regions involved in each, as a substantial proportion of white matter microstructural properties shows substantial commonality across these pathways (31). Scores of the first unrotated component of FA and MD were similarly extracted and set as dependent variables in general linear modelling, as above. Variance explained for each white matter tract subset was as follows: association fibres: 45.36% (FA), 50.76% (MD); thalamic radiations: 60.85% (FA), 73.40% (MD); projection fibres: 35.54% (FA), 29.28% (MD).

Lastly, we tested the association between PRS (both NETRIN1-PRS and genomic-PRS) and each individual white matter tract (N = 15). We used a repeated-effect linear model for the 12 bilateral tracts and a random-effect general linear model for the three unilateral tracts.

False discovery rate correction was applied separately for the 15 individual tracts and for global and tract category values.

Permutation analysis

In order to establish that the effect of the NETRIN1 pathway-derived PRS on WM integrity as measured by FA and MD was not due to chance, a circular genomic permutation was applied to the pathway SNP genotypes (32). This was done by placing all SNPs in the whole genome (excluding those in the NETRIN1 pathway) in a circular genome, according to their location. We then circularly permuted 1000 SNP lists with the same set size as the NETRIN1 pathway. We then created 1000 PRS lists which were then fitted in linear mixed-effects and general linear models, depending on the white matter tract tested, and their association with five white matter tracts and one tract category, found to be significantly associated with NETRIN1, was tested.

Results

Results presented below are significant specifically to each pathway. White matter tracts showing a significant association with both the NETRIN1-PRS and the genomic-PRS pathways are described in the supplementary materials (pgs. 27-28). Results for all individual white matter tracts, tract categories and global measures can be found in tables 1-4 and figures 1-4.

The effect of unpruned NETRIN1-PRS & genomic-PRS on measures of white matter integrity – FA (N = 6,401)

Global measures

We first tested the effect of NETRIN1-PRS and genomic-PRS on global FA (gFA). Lower gFA was significantly associated with higher genomic-PRS ($\beta = -0.033$, $p_{\text{corrected}} = 0.011$) only.

Tract categories

We then tested the association between NETRIN1-PRS and Genomic-PRS and three subsets of white matter tracts (association fibres, thalamic radiations and projection fibres). Significantly lower FA values in projection fibres were found for genomic-PRS ($\beta = -0.028$, $p_{\text{corrected}} = 0.020$) only.

Individual white matter tracts

Lastly, we investigated the effect of NETRIN1-PRS and genomic-PRS on WM integrity in 15 individual white matter tracts. NETRIN1-PRS, but not genomic-PRS, was associated with significantly lower FA in the superior longitudinal fasciculus ($\beta = -0.035$, $p_{\text{corrected}} = 0.029$).

In the genomic-PRS, we found significantly lower FA in the forceps major ($\beta = -0.031$, $p_{\text{corrected}} = 0.043$), forceps minor ($\beta = -0.031$, $p_{\text{corrected}} = 0.043$) and uncinata fasciculus ($\beta = -0.031$, $p_{\text{corrected}} = 0.043$). None of these tracts showed significant associations with NETRIN1-PRS.

The effect of unpruned NETRIN1-PRS & genomic-PRS on measures of white matter integrity – MD (N = 6,390)

Tract categories

MD values for association fibres ($\beta = 0.041$, $p_{\text{corrected}} = 0.001$) and projection fibres ($\beta = 0.028$, $p_{\text{corrected}} = 0.023$) were found to be significantly higher for genomic-PRS, but not NETRIN1-PRS. MD values for thalamic radiations were found to be significantly higher in the NETRIN1-PRS ($\beta = 0.029$, $p_{\text{corrected}} = 0.021$), whereas there was no significant association with genomic-PRS.

Individual white matter tracts

Within the 15 individual white matter tracts, we found numerous areas significantly associated with both the NETRIN1-PRS and genomic-PRS. With regards to NETRIN1-PRS, MD values were significantly higher in the inferior longitudinal fasciculus ($\beta = 0.029$, $p_{\text{corrected}} = 0.043$), superior longitudinal fasciculus ($\beta = 0.034$, $p_{\text{corrected}} = 0.039$), and in the anterior ($\beta = 0.025$, $p_{\text{corrected}} = 0.046$) and superior ($\beta = 0.027$, $p_{\text{corrected}} = 0.043$) thalamic radiations. All of these significant associations were specific for NETRIN1-PRS.

In the genomic-PRS, we found significantly higher MD values in the cingulate gyrus ($\beta = 0.035$, $p_{\text{corrected}} = 0.013$) and parahippocampal ($\beta = 0.032$, $p_{\text{corrected}} = 0.014$) part of cingulum and in the uncinata fasciculus ($\beta = 0.029$, $p_{\text{corrected}} = 0.018$).

Permutation analysis

NETRIN1-PRS, but not genomic-PRS, were found to be individually significantly associated with white matter microstructure in the following white matter tracts: superior longitudinal fasciculus as measured by lower FA; superior and inferior longitudinal fasciculus and anterior and superior thalamic radiations, as well as thalamic radiations tract category, as measured by higher MD. Therefore, we additionally performed a circular genomic permutation analysis and found that the variance explained by NETRIN1-PRS in these tracts was significantly higher than expected by chance (table 5).

Discussion

In the present study, we aimed to investigate whether PRS calculated from the NETRIN1 signalling pathway are significantly and specifically associated with WM integrity while simultaneously modelling genomic-PRS in more than 6,000 individuals. We found significant differences in white matter integrity in both NETRIN1-PRS and genomic-PRS, for both FA and MD values. Regarding FA values, for NETRIN1-PRS, but not for genomic-PRS, a significant association was observed in the superior longitudinal fasciculus. NETRIN1-PRS alone were significantly associated with higher generalised thalamic radiations as measured by MD, as well as higher MD in the superior and inferior longitudinal fasciculus, and the anterior and superior thalamic radiations. Genomic-PRS were also significantly associated with FA and MD values in several tracts.

One of the main findings in our paper was both a reduction of FA and an increase of MD in the SLF in relation to NETRIN1-PRS. The SLF, a tract in association fibres, connects the frontal, temporal, parietal and occipital lobes, and has been shown to be highly involved in MDD (38; 39). FA reductions in the SLF have also been found in previous studies combining genetic and neuroimaging techniques (35), further indicating that the tract might be an important biomarker of MDD. In addition to this finding, we also found an increase in MD values in the ILF, a tract connecting the temporal and occipital lobes. Key areas in these two lobes include the amygdala and hippocampus, which are known to be implicated in emotion processing, a process which is disrupted in MDD (40). Previous studies have found disrupted white matter integrity in this tract in association with MDD using FA, indicating that it may play an important role in the pathophysiology of MDD (35).

We also found an MD increase in the thalamic radiations tract category. Thalamic radiations connect the thalamus with numerous cortical areas (33), and are connected to

various cognitive processes, such as attention and wakefulness (34). Thalamocortical axons play an important role during development, as their projection from the dorsal thalamus (DT) transmit sensory information to the neocortex (33). Thalamic radiations have previously been linked to MDD in numerous studies. For instance, a decrease in FA was found in the TR subset in a large UKB sample comparing 335 MDD patients with 754 healthy individuals (20). This tract subset was also found to be significantly associated with higher PRS, indicating that there is a link between the sets of tracts and a potential genetic predisposition to MDD (35).

NETRIN1, and its receptor DCC, one of the genes in the NETRIN1-pathway, have been previously implicated in thalamic axonal growth. NETRIN1 promotes growth of thalamocortical axons by binding to and activating DCC, which is expressed in the DT. Moreover, NETRIN1 has been shown to enhance axonal growth in explants of the DT, as well as providing guidance from the DT to the cortex (33). It has also been found that serotonin, which is highly implicated in MDD, modulates the effect of NETRIN1 on embryonic thalamocortical axons (33; 34; 36). The active involvement of NETRIN1 in thalamocortical axonal growth, therefore, may explain our findings, and further confirms that there is a potential link between a biological pathway and specific neurobiological markers in MDD.

Several other tracts also showed a significant association of FA (individually in forceps major and minor and uncinate fasciculus, and in global measures of FA and projection fibres) and MD (individually in cingulate part of the cingulum, parahippocampal part of cingulum and uncinate fasciculus, and in global measures of association and projection fibres) with genomic-PRS, most of which have also been previously associated with MDD. (20, 35). This evidence further confirms that there is an association between genetic predisposition to MDD

and disruptions in white matter integrity, also for variants that lie outside the NETRIN1-DCC pathway. As such, these findings suggest that both PRS lists affect integrity across the white matter tracts, each with localized, pronounced effect in specific tracts.

The current study has several strengths and a few potential limitations. First of all, it is the largest combined genetic and neuroimaging study investigating the effect of PRS derived from a specific biological pathway on white matter integrity, to our knowledge. Moreover, our analysis consisted of a population-based sample of ambulant individuals recruited to UKB. Our findings might therefore be robust and generalizable to other samples within a certain age range, although studies such as UKB are not immune to biases associated with study participation, such as collider bias (37).

In addition to the large sample, the fact that NETRIN1-PRS are derived from only 43 genes, comprising approximately 0.215% of the genes in the whole genome ($N = \sim 20,000$) suggests that MDD risk associated variation exerts a disproportionate influence on white matter microstructure. Our findings are also further supported by permutation analysis. The association between the NETRIN1 pathway and white matter integrity is therefore likely to reflect the importance of a specific pathway in the pathophysiology of MDD.

The NETRIN1 signaling pathway has previously been found to be implicated in MDD (14). In the current study, we were able to find specific neurobiological structural connectivity markers associated with this biological pathway. To our knowledge, the current study is the first one to note an association between PRS derived specifically from the NETRIN1 signaling pathway and several white matter tracts in a large genetic and neuroimaging dataset. This indicates that these brain structures may be involved in the manifestation of genetic risk of MDD and ultimately the aetiology of the disorder.

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Legends

Table 1. The effect of NETRIN1-PRS & genomic-PRS at PRS threshold 0.5 on individual white matter tracts (FA values). Statistically significant p-values after false discovery rate correction for each pathway individually are shown in bold. R2 = estimate of variance explained by each pathway in %.

Table 2. The effect of NETRIN1-PRS & genomic-PRS at PRS threshold 0.5 on global FA and 3 white matter tract categories. Statistically significant p-values after false discovery rate correction for each pathway individually are shown in bold. R2 = estimate of variance explained by each pathway in %.

Table 3. The effect of NETRIN1-PRS & genomic-PRS at PRS threshold 0.5 on individual white matter tracts (MD values). Statistically significant p-values after false discovery rate correction for each pathway individually are shown in bold. R2 = estimate of variance explained by each pathway in %.

Table 4. The effect of NETRIN1-PRS & genomic-PRS at PRS threshold 0.5 on global MD and 3 white matter tract subsets. Statistically significant p-values after false discovery rate correction for each pathway individually are shown in bold. R2 = estimate of variance explained by each pathway in %.

Table 5. Permutation results for NETRIN1-PRS at PRS threshold 0.5 on 5 significant white matter tracts and one significant tract category.

Figures 1a & 1b. The effect of NETRIN1-PRS & genomic-PRS on FA values of white matter tracts. The x-axis indicates the standardised effect size of each pathway's PRS and the y-axis indicates the white matter tracts. The legend indicates the tract category belonging to each white matter tract. The error bar represents standard deviation of mean.

Figure 2. The effect of NETRIN1-PRS & genomic-PRS on FA values of tract categories and global FA. The x-axis indicates the standardised effect size of each pathway's PRS and the y-axis indicates the tract categories. The error bar represents standard deviation of mean.

Figures 3a & 3b. The effect of NETRIN1-PRS & genomic-PRS on MD values of white matter tracts. The x-axis indicates the standardised effect size of each pathway's PRS and the y-axis indicates the white matter tracts. The legend indicates the tract category belonging to each white matter tract. The error bar represents standard deviation of mean.

Figure 4. The effect of NETRIN1-PRS & genomic-PRS on MD values of tract categories and global MD. The x-axis indicates the standardised effect size of each pathway's PRS and the y-axis indicates the tract categories. The error bar represents standard deviation of mean.

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	White matter tracts	NETRIN1-PRS						genomic-PRS							
		Effect size (β)	Standard deviation	t value	p value	p corrected (FDR)	R2	Effect size (β)	Standard deviation	t value	p value	p corrected (FDR)	R2		
Association fibres	Cingulate gyrus part of cingulum	-0.025	0.011	-	2.323	0.020	0.152	0.062	-0.019	0.011	-	1.817	0.069	0.115	0.038
	Parahippocampal part of cingulum	-0.008	0.011	-	0.780	0.435	0.544	0.007	-0.020	0.011	-	1.873	0.061	0.115	0.040
	Inferior fronto-occipital fasciculus	-0.023	0.011	-	1.997	0.046	0.172	0.053	-0.028	0.012	-	2.409	0.016	0.060	0.076
	Inferior longitudinal fasciculus	-0.023	0.011	-	2.029	0.043	0.172	0.054	-0.024	0.012	-	2.056	0.040	0.115	0.056
	Superior longitudinal fasciculus	-0.036	0.012	-	3.093	0.002	0.030	0.128	-0.023	0.012	-	1.988	0.047	0.115	0.053
	Uncinate fasciculus	-0.019	0.011	-	1.747	0.081	0.202	0.102	-0.032	0.011	-	2.954	0.003	0.043	0.102
Thalamic radiations	Anterior thalamic radiation	-0.022	0.011	-	1.900	0.057	0.172	0.048	-0.015	0.011	-	1.310	0.190	0.238	0.023
	Posterior thalamic radiations	-0.014	0.011	-	1.267	0.205	0.308	0.020	-0.022	0.011	-	1.929	0.054	0.115	0.047
	Superior thalamic radiation	-0.006	0.012	-	0.493	0.622	0.718	0.003	-0.015	0.012	-	1.246	0.213	0.244	0.022
Projection fibres	Acoustic radiation	0.003	0.011	-	0.306	0.759	0.814	0.001	-0.013	0.011	-	1.207	0.228	0.244	0.016
	Corticospinal tract	0.002	0.011	-	0.173	0.863	0.863	0.000	-0.018	0.011	-	1.632	0.103	0.154	0.034
	Medial lemniscus	-0.009	0.010	-	0.842	0.400	0.544	0.008	-0.003	0.010	-	0.249	0.803	0.803	0.001
	Forceps major	-0.016	0.012	-	1.301	0.193	0.308	0.024	-0.032	0.012	-	2.626	0.009	0.043	0.100
	Forceps minor	-0.018	0.012	-	1.496	0.135	0.262	0.032	-0.032	0.012	-	2.628	0.009	0.043	0.099
	Middle cerebellar peduncle	-0.018	0.012	-	1.476	0.140	0.262	0.032	-0.019	0.012	-	1.536	0.125	0.170	0.035

Table 1. The effect of NETRIN1-PRS & genomic-PRS at PRS threshold 0.5 on individual white matter tracts (FA values). Statistically significant p-values after false discovery rate correction for each pathway individually are shown in bold. R2 = estimate of variance explained by each pathway in %.

	NETRIN1-PRS						genomic-PRS					
	Effect size(β)	Standard deviation	t value	p value	P corrected (FDR)	R2	Effect size(β)	Standard deviation	t value	p value	P corrected (FDR)	R2
gFA	-0.026	0.012	-2.197	0.028	0.056	0.068	-0.033	0.012	-2.769	0.006	0.011	0.109
Association fibres	-0.033	0.012	-2.762	0.006	0.023	0.107	-0.034	0.012	-2.836	0.005	0.011	0.113
Thalamic radiations	-0.018	0.012	-1.482	0.138	0.185	0.032	-0.022	0.012	-1.855	0.064	0.064	0.050
Projection fibres	-0.011	0.012	-0.904	0.366	0.366	0.012	-0.029	0.012	-2.415	0.016	0.021	0.083

Table 2. The effect of NETRIN1-PRS & genomic-PRS at PRS threshold 0.5 on global FA and 3 white matter tract categories. Statistically significant p-values after false discovery rate correction for each pathway individually are shown in bold. R2 = estimate of variance explained by each pathway in %.

	White matter tracts	NETRIN1-PRS						genomic-PRS					
		Effect size (β)	Standard deviation	t value	p value	p corrected (FDR)	R2	Effect size (β)	Standard deviation	t value	p value	p corrected (FDR)	R2
Association fibres	Cingulate gyrus part of cingulum	0.020	0.011	1.877	0.061	0.130	0.040	0.035	0.011	3.317	0.001	0.014	0.124
	Parahippocampal part of cingulum	0.002	0.011	0.175	0.861	0.861	0.000	0.033	0.011	3.109	0.002	0.014	0.107
	Inferior fronto-occipital fasciculus	0.027	0.011	2.461	0.014	0.047	0.075	0.031	0.011	2.807	0.005	0.019	0.098
	Inferior longitudinal fasciculus	0.029	0.011	2.625	0.009	0.043	0.086	0.025	0.011	2.216	0.027	0.067	0.061
	Superior longitudinal fasciculus	0.034	0.011	3.009	0.003	0.039	0.116	0.024	0.011	2.133	0.033	0.071	0.058
	Uncinate fasciculus	0.018	0.010	1.698	0.090	0.168	0.085	0.029	0.010	2.815	0.005	0.019	0.084
Thalamic radiations	Anterior thalamic radiation	0.025	0.011	2.420	0.016	0.047	0.065	0.021	0.011	2.028	0.043	0.080	0.046
	Posterior thalamic radiations	0.025	0.011	2.326	0.020	0.050	0.062	0.002	0.011	0.157	0.876	0.876	0.000
	Superior thalamic radiation	0.027	0.010	2.758	0.006	0.043	0.074	0.018	0.010	1.771	0.077	0.096	0.031
Projection fibres	Acoustic radiation	0.004	0.010	0.375	0.708	0.772	0.002	0.019	0.011	1.853	0.064	0.087	0.038
	Corticospinal tract	0.016	0.011	1.399	0.162	0.221	0.025	0.022	0.011	1.921	0.055	0.082	0.047
	Medial lemniscus	0.004	0.011	0.357	0.721	0.772	0.001	0.004	0.011	0.396	0.692	0.741	0.002
	Forceps major	0.018	0.012	1.495	0.135	0.203	-0.026	0.028	0.012	2.362	0.018	0.055	0.019
	Forceps minor	0.019	0.012	1.640	0.101	0.168	-0.063	0.023	0.012	1.958	0.050	0.082	-0.051
	Middle cerebellar peduncle	0.013	0.012	1.058	0.290	0.363	0.016	0.010	0.012	0.852	0.394	0.455	0.010

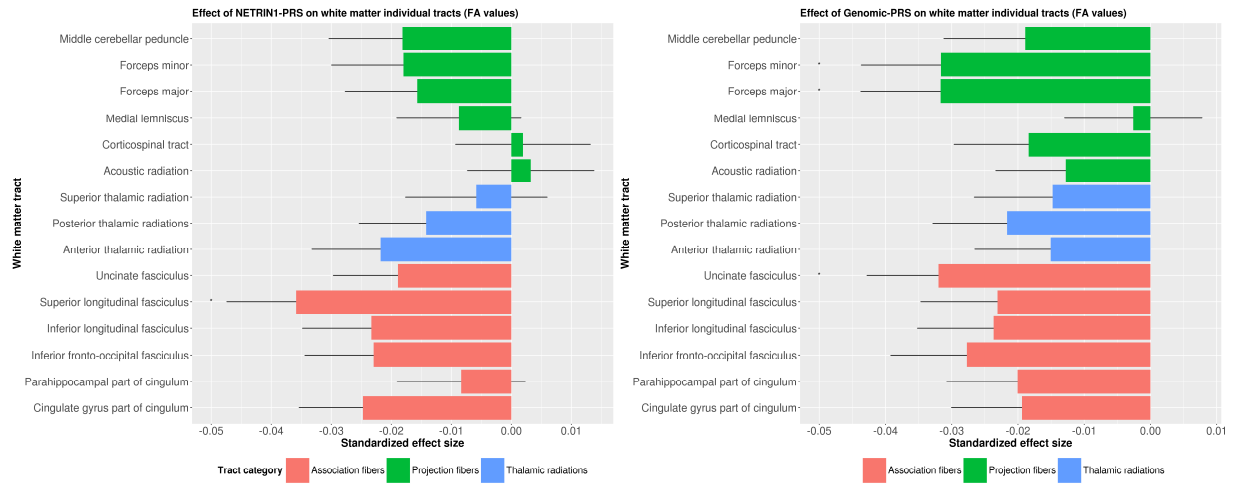
Table 3. The effect of NETRIN1-PRS & genomic-PRS at PRS threshold 0.5 on individual white matter tracts (MD values). Statistically significant p-values after false discovery rate correction for each pathway individually are shown in bold. R2 = estimate of variance explained by each pathway in %.

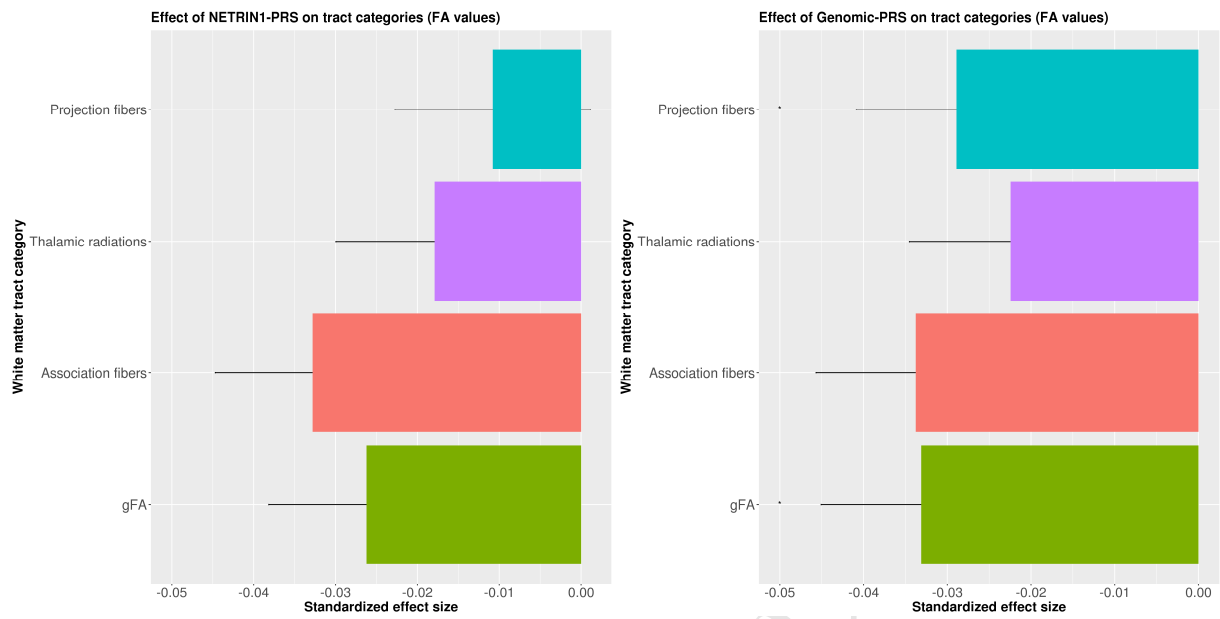
	NETRIN1-PRS						genomic-PRS					
	Effect size(β)	Standard deviation	t value	p value	P corrected (FDR)	R2	Effect size(β)	Standard deviation	t value	p value	P corrected (FDR)	R2
gMD	0.028	0.011	2.417	0.016	0.031	0.076	0.034	0.011	2.924	0.003	0.007	0.111
Association fibres	0.022	0.012	1.897	0.058	0.077	0.048	0.042	0.012	3.591	0.000	0.001	0.172
Thalamic radiations	0.030	0.011	2.785	0.005	0.021	0.089	0.013	0.011	1.232	0.218	0.218	0.017
Projection fibres	0.021	0.012	1.766	0.077	0.077	0.045	0.029	0.012	2.380	0.017	0.023	0.081

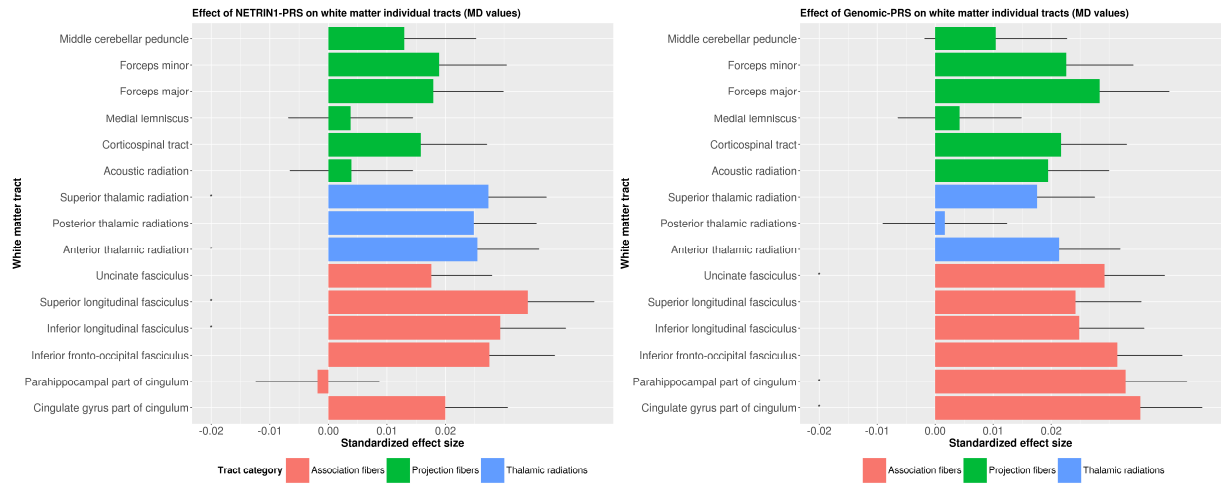
Table 4. The effect of NETRIN1-PRS & genomic-PRS at PRS threshold 0.5 on global MD and 3 white matter tract subsets. Statistically significant p-values after false discovery rate correction for each pathway individually are shown in bold. R2 = estimate of variance explained by each pathway in %.

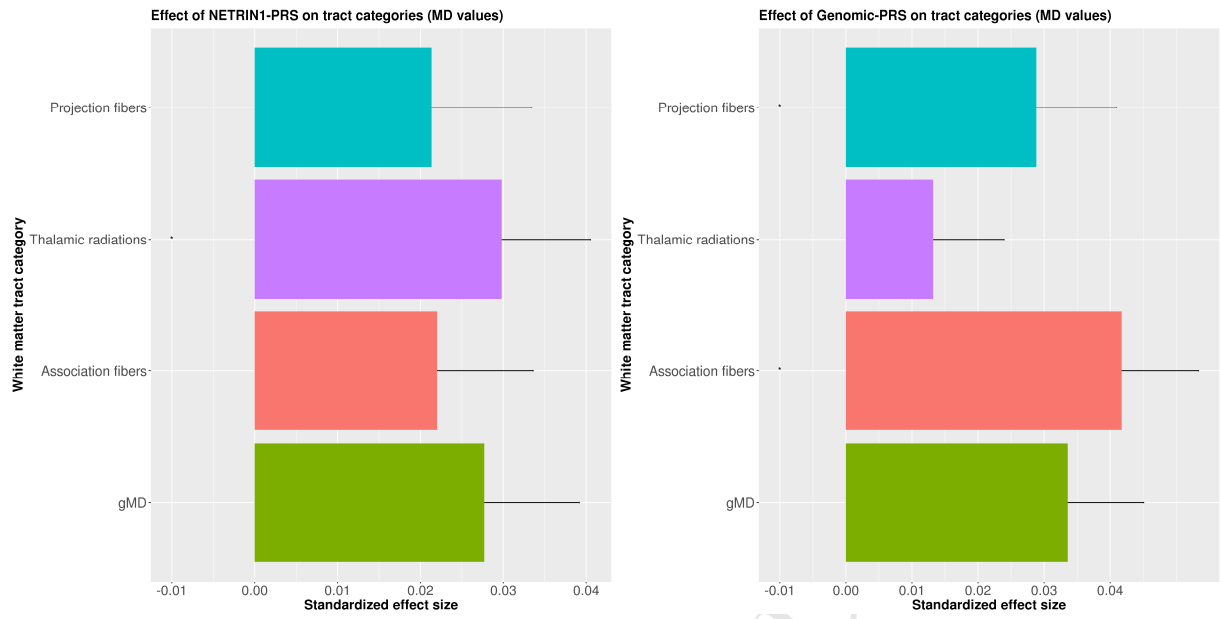
White matter tract	Effect size of regression NETRIN1 pathway	Regression NETRIN1 pathway t-score	NETRIN1 calculated permutation p value
Superior longitudinal fasciculus (FA)	-0.035	-3.093	0.004
Superior longitudinal fasciculus (MD)	0.034	3.008	0.004
Inferior longitudinal fasciculus (MD)	0.029	2.624	0.014
Anterior thalamic radiations (MD)	0.025	2.419	0.023
Superior thalamic radiations (MD)	0.027	2.757	0.007
Thalamic radiations (MD)	0.029	2.785	0.008

Table 5. Permutation results for NETRIN1-PRS at PRS threshold 0.5 on 5 significant white matter tracts and one significant tract category.









Association of Whole-genome and NETRIN1 Signaling Pathway-derived Polygenic Risk Scores for Major Depressive Disorder and White Matter Microstructure in UK Biobank

Supplemental Information

Supplementary notes

- Demographic data concerning complete dataset of individuals with DTI values
- Descriptive statistics of imaging phenotype
- NETRIN1 signalling pathway gene list
- Demographic data and FA descriptive statistics of individuals excluded from the study (N = 19)
- Demographic data and MD descriptive statistics of individuals excluded from the study (N = 30)
- Statistical analysis of FA and MD values containing:
 1. Unpruned NETRIN1- and genomic-PRS with outliers excluded (6,401 for FA and 6,390 for MD) at all 5 thresholds (0.01, 0.05, 0.1, 0.5, 1) and full sample (6,420) at threshold 0.5
 2. Pruned NETRIN1- and Genomic-PRS with outliers excluded (6,401 for FA and 6,390 for MD) at all 5 thresholds (0.01, 0.05, 0.1, 0.5, 1) and full sample (6,420) at threshold 0.5
- White matter tracts significantly associated with both NETRIN1-PRS and genomic-PRS.
 1. Fractional anisotropy
 2. Mean diffusivity
- Data analysis code – example

Supplementary tables

- Table S1. Descriptive statistics of FA values (mean and standard deviation). The full dataset contains 6,420 individuals, while the outliers-excluded dataset contains 6,401 individuals.
- Table S2. Descriptive statistics of MD values (mean and standard deviation). The full dataset contains 6,420 individuals, while the outliers-excluded dataset contains 6,390 individuals.
- Table S3. Gene list and brief gene description included in the NETRIN1 signalling pathway, composed of 43 genes.
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- Table S5. Descriptive statistics of MD values (mean and standard deviation) for individuals excluded from the study (N = 30).
- Table S6. The effect of unpruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on individual white matter tracts (FA) (N = 6,401).
- Table S7. The effect of unpruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on tract categories (FA) (N = 6,401).
- Table S8. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on individual white matter tracts (FA) (N = 6,420).
- Table S9. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on tract categories (FA) (N = 6,420).
- Table S10. The effect of unpruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on individual white matter tracts (MD) (N = 6,390).
- Table S11. The effect of unpruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on tract categories (MD) (N = 6,390).
- Table S12. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on individual white matter tracts (MD) (N = 6,420).
- Table S13. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on tract categories (MD) (N = 6,420).
- Table S14. The effect of pruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05,

0.1, 0.5 and 1 on individual white matter tracts (FA) (N = 6,401).

- Table S15. The effect of pruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on tract categories (FA) (N = 6,401).
- Table S16. The effect of pruned NETRIN1- and Genomic-PRS at threshold 0.5 on individual white matter tracts (FA) (N = 6,420).
- Table S17. The effect of pruned NETRIN1- and Genomic-PRS at threshold 0.5 on tract categories (FA) (N = 6,420).
- Table S18. The effect of pruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on individual white matter tracts (MD) (N = 6,390).
- Table S19. The effect of pruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on tract categories (MD) (N = 6,390).
- Table S20. The effect of pruned NETRIN1- and Genomic-PRS at threshold 0.5 on individual white matter tracts (MD) (N = 6,420).
- Table S21. The effect of pruned NETRIN1- and Genomic-PRS at threshold 0.5 on tract categories (MD) (N = 6,420).

Table S1. Descriptive statistics of FA values (mean and standard deviation). The full dataset contains 6,420 individuals, while the outliers-excluded dataset contains 6,401 individuals.

Demographic data concerning complete dataset of individuals with DTI values

Complete dataset (N = 6,420): N female = 3,345; N male = 3,075; mean age: 62.62 +/- 7.37 years; age range: 45.92 – 78.42

Descriptive statistics of imaging phenotype

Fractional Anisotropy	Full dataset (N = 6,420)		Outliers excluded dataset (N = 6,401)	
	Mean	SD	Mean	SD
White matter tract				
Cingulate gyrus part of cingulum (left)	0.535	0.035	0.535	0.033
Cingulate gyrus part of cingulum (right)	0.497	0.034	0.498	0.033
Parahippocampal part of cingulum (left)	0.314	0.029	0.314	0.028
Parahippocampal part of cingulum (right)	0.313	0.030	0.313	0.030
Inferior fronto-occipital fasciculus (left)	0.475	0.024	0.476	0.022
Inferior fronto-occipital fasciculus (right)	0.465	0.021	0.465	0.020
Inferior longitudinal fasciculus (left)	0.460	0.021	0.460	0.019
Inferior longitudinal fasciculus (right)	0.451	0.020	0.451	0.018
Superior longitudinal fasciculus (left)	0.440	0.022	0.440	0.020
Superior longitudinal fasciculus (right)	0.423	0.021	0.424	0.019
Uncinate fasciculus (left)	0.388	0.024	0.388	0.235
Uncinate fasciculus (right)	0.390	0.021	0.390	0.020
Anterior thalamic radiation (left)	0.399	0.019	0.399	0.017
Anterior thalamic radiation (right)	0.392	0.019	0.392	0.017
Posterior thalamic radiation (left)	0.458	0.022	0.458	0.020
Posterior thalamic radiation (right)	0.455	0.022	0.456	0.020
Superior thalamic radiation (left)	0.422	0.019	0.423	0.018
Superior thalamic radiation (right)	0.422	0.020	0.422	0.018
Acoustic radiation (left)	0.419	0.023	0.420	0.021
Acoustic radiation (right)	0.411	0.022	0.412	0.020
Corticospinal tract (left)	0.545	0.024	0.545	0.022
Corticospinal tract (right)	0.539	0.025	0.539	0.022
Medial lemniscus (left)	0.419	0.024	0.419	0.023
Medial lemniscus (right)	0.422	0.025	0.422	0.024
Forceps major	0.580	0.029	0.580	0.027
Forceps minor	0.465	0.022	0.465	0.020
Middle cerebellar peduncle	0.481	0.031	0.481	0.029

Table S2. Descriptive statistics of MD values (mean and standard deviation). The full dataset contains 6,420 individuals, while the outliers-excluded dataset contains 6,390 individuals.

Mean Diffusivity	Full dataset (N = 6,420)		Outliers excluded dataset (N = 6,390)	
	Mean	SD	Mean	SD
White matter tract				
Cingulate gyrus part of cingulum (left)	0.0007	0.00003	0.0007	0.00002
Cingulate gyrus part of cingulum (right)	0.0007	0.00003	0.0007	0.00002
Parahippocampal part of cingulum (left)	0.0008	0.00006	0.0008	0.00005
Parahippocampal part of cingulum (right)	0.0008	0.00006	0.0008	0.00005
Inferior fronto-occipital fasciculus (left)	0.0008	0.00003	0.0008	0.00003
Inferior fronto-occipital fasciculus (right)	0.0008	0.00003	0.0008	0.00003
Inferior longitudinal fasciculus (left)	0.0008	0.00003	0.0008	0.00003
Inferior longitudinal fasciculus (right)	0.0008	0.00003	0.0008	0.00003
Superior longitudinal fasciculus (left)	0.0007	0.00003	0.0007	0.00003
Superior longitudinal fasciculus (right)	0.0007	0.00003	0.0007	0.00003
Uncinate fasciculus (left)	0.0008	0.00004	0.0008	0.00003
Uncinate fasciculus (right)	0.0008	0.00003	0.0008	0.00003
Anterior thalamic radiation (left)	0.0007	0.00003	0.0007	0.00003
Anterior thalamic radiation (right)	0.0007	0.00003	0.0007	0.00003
Posterior thalamic radiation (left)	0.0008	0.00004	0.0008	0.00004
Posterior thalamic radiation (right)	0.0008	0.00004	0.0008	0.00004
Superior thalamic radiation (left)	0.0007	0.00003	0.0007	0.00002
Superior thalamic radiation (right)	0.0007	0.00003	0.0007	0.00002
Acoustic radiation (left)	0.0007	0.00004	0.0007	0.00003
Acoustic radiation (right)	0.0007	0.00004	0.0007	0.00003
Corticospinal tract (left)	0.0007	0.00002	0.0007	0.00002
Corticospinal tract (right)	0.0007	0.00002	0.0007	0.00002
Medial lemniscus (left)	0.0009	0.00004	0.0009	0.00003
Medial lemniscus (right)	0.0009	0.00004	0.0009	0.00003
Forceps major	0.0009	0.00005	0.0009	0.00005
Forceps minor	0.0008	0.00003	0.0008	0.00003
Middle cerebellar peduncle	0.0007	0.00006	0.0007	0.00006

Table S3. Gene list and brief gene description included in the NETRIN1 signalling pathway, composed of 43 genes.**NETRIN1 signalling pathway gene list**

Gene name	Description
UNC5D	unc-5 homolog D (<i>C. elegans</i>)
HFE2	hemochromatosis type 2 (juvenile)
DCC	deleted in colorectal carcinoma
DOCK1	dedicator of cytokinesis 1
UNC5B	unc-5 homolog B (<i>C. elegans</i>)
ABLIM3	actin binding LIM protein family, member 3
FYN	FYN oncogene related to SRC, FGR, YES
RGMB	RGM domain family, member B
ABLIM1	actin binding LIM protein 1
MYO10	myosin X
NCK1	NCK adaptor protein 1
NEO1	neogenin 1
PITPNA	phosphatidylinositol transfer protein, alpha
PLCG1	phospholipase C, gamma 1
PRKCQ	protein kinase C, theta
RGMA	RGM domain family, member A
TRPC7	transient receptor potential cation channel
PTK2	PTK2 protein tyrosine kinase 2
RAC1	ras-related C3 botulinum toxin substrate 1 precursor
NTN4	netrin 4
ROBO1	roundabout, axon guidance receptor, homolog 1
SIAH1	seven in absentia homolog 1 (<i>Drosophila</i>)
SIAH2	seven in absentia homolog 2 (<i>Drosophila</i>)
SLIT1	slit homolog 1 (<i>Drosophila</i>)
SLIT3	slit homolog 3 (<i>Drosophila</i>)
SRC	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene
TRIO	triple functional domain (PTPRF interacting)
TRPC3	transient receptor potential cation channel
TRPC4	transient receptor potential cation channel
TRPC5	transient receptor potential cation channel
TRPC6	transient receptor potential cation channel
LOC730030	---
LOC730221	---
LOC730335	---
LOC730221	---
LOC730030	---
EZR	ezrin
UNC5C	unc-5 homolog C (<i>C. elegans</i>)
WASL	Wiskott-Aldrich syndrome-like
UNC5A	unc-5 homolog A (<i>C. elegans</i>)
SLIT2	slit homolog 2 (<i>Drosophila</i>)
NTN1	netrin 1
CDC42	cell division cycle 42 (GTP binding protein)

Table S4. Descriptive statistics of FA values (mean and standard deviation) for individuals excluded from the study (N = 19).**Demographic data and FA descriptive statistics of individuals excluded from the study****(N = 19)**

N female = 11; N male = 8; mean age: 69.26 +/- 4.53 years; age range: 58.92 – 77.42

Fractional Anisotropy	Outlier dataset (N = 19)	
White matter tract	Mean	SD
Cingulate gyrus part of cingulum (left)	0.407	0.149
Cingulate gyrus part of cingulum (right)	0.388	0.144
Parahippocampal part of cingulum (left)	0.246	0.091
Parahippocampal part of cingulum (right)	0.254	0.095
Inferior fronto-occipital fasciculus (left)	0.354	0.127
Inferior fronto-occipital fasciculus (right)	0.354	0.127
Inferior longitudinal fasciculus (left)	0.348	0.124
Inferior longitudinal fasciculus (right)	0.338	0.122
Superior longitudinal fasciculus (left)	0.325	0.117
Superior longitudinal fasciculus (right)	0.309	0.112
Uncinate fasciculus (left)	0.296	0.106
Uncinate fasciculus (right)	0.301	0.107
Anterior thalamic radiation (left)	0.306	0.110
Anterior thalamic radiation (right)	0.306	0.109
Posterior thalamic radiation (left)	0.358	0.127
Posterior thalamic radiation (right)	0.350	0.126
Superior thalamic radiation (left)	0.335	0.119
Superior thalamic radiation (right)	0.336	0.120
Acoustic radiation (left)	0.324	0.116
Acoustic radiation (right)	0.320	0.116
Corticospinal tract (left)	0.436	0.156
Corticospinal tract (right)	0.431	0.155
Medial lemniscus (left)	0.353	0.127
Medial lemniscus (right)	0.353	0.130
Forceps major	0.460	0.166
Forceps minor	0.346	0.125
Middle cerebellar peduncle	0.381	0.171

Table S5. Descriptive statistics of MD values (mean and standard deviation) for individuals excluded from the study (N = 30).**Demographic data and MD descriptive statistics of individuals excluded from the study****(N = 30)**

N female = 18; N male = 12; mean age: 70.29 +/- 4.66 years; age range: 58.92 – 77.42

Mean Diffusivity	Outlier dataset (N = 30)	
	Mean	SD
White matter tract		
Cingulate gyrus part of cingulum (left)	0.0007	0.0002
Cingulate gyrus part of cingulum (right)	0.0007	0.0002
Parahippocampal part of cingulum (left)	0.0009	0.0002
Parahippocampal part of cingulum (right)	0.0009	0.0002
Inferior fronto-occipital fasciculus (left)	0.0008	0.0002
Inferior fronto-occipital fasciculus (right)	0.0008	0.0002
Inferior longitudinal fasciculus (left)	0.0008	0.0002
Inferior longitudinal fasciculus (right)	0.0008	0.0002
Superior longitudinal fasciculus (left)	0.0008	0.0002
Superior longitudinal fasciculus (right)	0.0008	0.0002
Uncinate fasciculus (left)	0.0008	0.0002
Uncinate fasciculus (right)	0.0008	0.0002
Anterior thalamic radiation (left)	0.0008	0.0002
Anterior thalamic radiation (right)	0.0008	0.0002
Posterior thalamic radiation (left)	0.0009	0.0002
Posterior thalamic radiation (right)	0.0009	0.0002
Superior thalamic radiation (left)	0.0007	0.0002
Superior thalamic radiation (right)	0.0007	0.0002
Acoustic radiation (left)	0.0008	0.0002
Acoustic radiation (right)	0.0008	0.0002
Corticospinal tract (left)	0.0007	0.0002
Corticospinal tract (right)	0.0007	0.0002
Medial lemniscus (left)	0.0008	0.0002
Medial lemniscus (right)	0.0008	0.0002
Forceps major	0.0009	0.0002
Forceps minor	0.0008	0.0002
Middle cerebellar peduncle	0.0007	0.0002

Table S6. The effect of unpruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on individual white matter tracts (FA) (N = 6,401).**Statistical analysis of FA and MD values containing:**

Unpruned NETRIN1- and genomic-PRS with outliers included (6,420) and outliers excluded (6,401 for FA and 6,390 for MD) at all 5 thresholds (0.01, 0.05, 0.1, 0.5, 1)

	Value	Std. Error	t-value	p-value
PGRS THRESHOLD: 0.01				
NETRIN1 acoustic_radiation	-0.002	0.011	-0.166	0.868
NETRIN1 anterior_thalamic_radiation	-0.021	0.011	-1.833	0.067
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.013	0.011	-1.255	0.209
NETRIN1 parahippocampal_part_of_cingulum	-0.006	0.011	-0.526	0.599
NETRIN1 corticospinal_tract	-0.019	0.011	-1.701	0.089
NETRIN1 inferior_fronto_occipital_fasciculus	-0.019	0.012	-1.647	0.100
NETRIN1 inferior_longitudinal_fasciculus	-0.021	0.012	-1.813	0.070
NETRIN1 medial_lemniscus	-0.008	0.010	-0.735	0.462
NETRIN1 posterior_thalamic_radiation	-0.011	0.011	-0.981	0.326
NETRIN1 superior_longitudinal_fasciculus	-0.026	0.012	-2.254	0.024
NETRIN1 superior_thalamic_radiation	-0.015	0.012	-1.251	0.211
NETRIN1 uncinate_fasciculus	-0.018	0.011	-1.680	0.093
NETRIN1 bl.FA.wm.forceps_major	-0.017	0.012	-1.409	0.159
NETRIN1 bl.FA.wm.forceps_minor	-0.011	0.012	-0.934	0.351
NETRIN1 bl.FA.wm.middle_cerebellar_peduncle	-0.029	0.012	-2.333	0.020
Genomic acoustic_radiation	-0.011	0.011	-1.033	0.301
Genomic anterior_thalamic_radiation	-0.015	0.012	-1.315	0.188
Genomic cingulate_gyrus_part_of_cingulum	-0.016	0.011	-1.528	0.127
Genomic parahippocampal_part_of_cingulum	-0.019	0.011	-1.779	0.075
Genomic corticospinal_tract	-0.008	0.011	-0.666	0.505
Genomic inferior_fronto_occipital_fasciculus	-0.023	0.012	-2.008	0.045
Genomic inferior_longitudinal_fasciculus	-0.023	0.012	-1.959	0.050
Genomic medial_lemniscus	0.003	0.010	0.306	0.760
Genomic posterior_thalamic_radiation	-0.021	0.011	-1.873	0.061
Genomic superior_longitudinal_fasciculus	-0.026	0.012	-2.244	0.025
Genomic superior_thalamic_radiation	-0.010	0.012	-0.867	0.386
Genomic uncinate_fasciculus	-0.028	0.011	-2.545	0.011
Genomic bl.FA.wm.forceps_major	-0.037	0.012	-3.042	0.002
Genomic bl.FA.wm.forceps_minor	-0.031	0.012	-2.600	0.009
Genomic bl.FA.wm.middle_cerebellar_peduncle	-0.009	0.012	-0.730	0.465
PGRS THRESHOLD: 0.05				
NETRIN1 acoustic_radiation	0.009	0.011	0.819	0.413
NETRIN1 anterior_thalamic_radiation	-0.015	0.011	-1.282	0.200
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.011	0.011	-1.065	0.287
NETRIN1 parahippocampal_part_of_cingulum	-0.013	0.011	-1.197	0.232
NETRIN1 corticospinal_tract	-0.003	0.011	-0.276	0.782

	Value	Std. Error	t-value	p-value
NETRIN1 inferior_fronto_occipital_fasciculus	-0.005	0.011	-0.473	0.636
NETRIN1 inferior_longitudinal_fasciculus	-0.010	0.011	-0.841	0.400
NETRIN1 medial_lemniscus	-0.005	0.010	-0.456	0.649
NETRIN1 posterior_thalamic_radiation	-0.002	0.011	-0.205	0.838
NETRIN1 superior_longitudinal_fasciculus	-0.015	0.012	-1.265	0.206
NETRIN1 superior_thalamic_radiation	-0.001	0.012	-0.049	0.961
NETRIN1 uncinata_fasciculus	-0.009	0.011	-0.876	0.381
NETRIN1 bl.FA.wm.forceps_major	-0.008	0.012	-0.644	0.520
NETRIN1 bl.FA.wm.forceps_minor	-0.005	0.012	-0.397	0.691
NETRIN1 bl.FA.wm.middle_cerebellar_peduncle	-0.018	0.012	-1.461	0.144
Genomic acoustic_radiation	-0.012	0.011	-1.151	0.250
Genomic anterior_thalamic_radiation	-0.017	0.011	-1.459	0.145
Genomic cingulate_gyrus_part_of_cingulum	-0.019	0.011	-1.739	0.082
Genomic parahippocampal_part_of_cingulum	-0.019	0.011	-1.771	0.077
Genomic corticospinal_tract	-0.012	0.011	-1.037	0.300
Genomic inferior_fronto_occipital_fasciculus	-0.026	0.012	-2.292	0.022
Genomic inferior_longitudinal_fasciculus	-0.026	0.012	-2.252	0.024
Genomic medial_lemniscus	0.000	0.010	0.037	0.970
Genomic posterior_thalamic_radiation	-0.026	0.011	-2.357	0.018
Genomic superior_longitudinal_fasciculus	-0.029	0.012	-2.500	0.012
Genomic superior_thalamic_radiation	-0.015	0.012	-1.296	0.195
Genomic uncinata_fasciculus	-0.030	0.011	-2.725	0.006
Genomic bl.FA.wm.forceps_major	-0.037	0.012	-3.083	0.002
Genomic bl.FA.wm.forceps_minor	-0.034	0.012	-2.834	0.005
Genomic bl.FA.wm.middle_cerebellar_peduncle	-0.012	0.012	-0.983	0.326
PGRS THRESHOLD: 0.1				
NETRIN1 acoustic_radiation	0.005	0.011	0.443	0.658
NETRIN1 anterior_thalamic_radiation	-0.018	0.011	-1.580	0.114
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.016	0.011	-1.528	0.127
NETRIN1 parahippocampal_part_of_cingulum	-0.006	0.011	-0.580	0.562
NETRIN1 corticospinal_tract	-0.004	0.011	-0.314	0.753
NETRIN1 inferior_fronto_occipital_fasciculus	-0.013	0.011	-1.090	0.276
NETRIN1 inferior_longitudinal_fasciculus	-0.013	0.012	-1.091	0.275
NETRIN1 medial_lemniscus	-0.016	0.010	-1.569	0.117
NETRIN1 posterior_thalamic_radiation	-0.005	0.011	-0.481	0.631
NETRIN1 superior_longitudinal_fasciculus	-0.024	0.012	-2.065	0.039
NETRIN1 superior_thalamic_radiation	-0.010	0.012	-0.827	0.408
NETRIN1 uncinata_fasciculus	-0.008	0.011	-0.756	0.450
NETRIN1 bl.FA.wm.forceps_major	-0.014	0.012	-1.145	0.252
NETRIN1 bl.FA.wm.forceps_minor	-0.011	0.012	-0.934	0.350
NETRIN1 bl.FA.wm.middle_cerebellar_peduncle	-0.013	0.012	-1.049	0.294
Genomic acoustic_radiation	-0.012	0.011	-1.147	0.251
Genomic anterior_thalamic_radiation	-0.014	0.011	-1.186	0.236
Genomic cingulate_gyrus_part_of_cingulum	-0.018	0.011	-1.699	0.089

	Value	Std. Error	t-value	p-value
Genomic parahippocampal_part_of_cingulum	-0.017	0.011	-1.552	0.121
Genomic corticospinal_tract	-0.016	0.011	-1.379	0.168
Genomic inferior_fronto_occipital_fasciculus	-0.025	0.012	-2.177	0.030
Genomic inferior_longitudinal_fasciculus	-0.024	0.012	-2.121	0.034
Genomic medial_lemniscus	0.001	0.010	0.139	0.890
Genomic posterior_thalamic_radiation	-0.022	0.011	-2.002	0.045
Genomic superior_longitudinal_fasciculus	-0.026	0.012	-2.267	0.023
Genomic superior_thalamic_radiation	-0.014	0.012	-1.188	0.235
Genomic uncinate_fasciculus	-0.032	0.011	-2.915	0.004
Genomic bl.FA.wm.forceps_major	-0.033	0.012	-2.753	0.006
Genomic bl.FA.wm.forceps_minor	-0.031	0.012	-2.572	0.010
Genomic bl.FA.wm.middle_cerebellar_peduncle	-0.018	0.012	-1.465	0.143
PGRS THRESHOLD: 1				
NETRIN1 acoustic_radiation	0.003	0.011	0.294	0.769
NETRIN1 anterior_thalamic_radiation	-0.023	0.011	-2.051	0.040
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.029	0.011	-2.720	0.007
NETRIN1 parahippocampal_part_of_cingulum	-0.007	0.011	-0.692	0.489
NETRIN1 corticospinal_tract	0.001	0.011	0.120	0.905
NETRIN1 inferior_fronto_occipital_fasciculus	-0.024	0.011	-2.070	0.039
NETRIN1 inferior_longitudinal_fasciculus	-0.023	0.011	-1.978	0.048
NETRIN1 medial_lemniscus	-0.008	0.010	-0.757	0.449
NETRIN1 posterior_thalamic_radiation	-0.015	0.011	-1.360	0.174
NETRIN1 superior_longitudinal_fasciculus	-0.035	0.012	-3.017	0.003
NETRIN1 superior_thalamic_radiation	-0.006	0.012	-0.517	0.605
NETRIN1 uncinate_fasciculus	-0.019	0.011	-1.799	0.072
NETRIN1 forceps_major	-0.016	0.012	-1.333	0.183
NETRIN1 forceps_minor	-0.018	0.012	-1.537	0.124
NETRIN1 middle_cerebellar_peduncle	-0.016	0.012	-1.294	0.196
Genomic acoustic_radiation	-0.013	0.011	-1.230	0.219
Genomic anterior_thalamic_radiation	-0.016	0.011	-1.386	0.166
Genomic cingulate_gyrus_part_of_cingulum	-0.021	0.011	-1.943	0.052
Genomic parahippocampal_part_of_cingulum	-0.022	0.011	-2.022	0.043
Genomic corticospinal_tract	-0.018	0.011	-1.604	0.109
Genomic inferior_fronto_occipital_fasciculus	-0.028	0.012	-2.444	0.015
Genomic inferior_longitudinal_fasciculus	-0.025	0.012	-2.135	0.033
Genomic medial_lemniscus	-0.004	0.010	-0.401	0.689
Genomic posterior_thalamic_radiation	-0.022	0.011	-1.923	0.054
Genomic superior_longitudinal_fasciculus	-0.022	0.012	-1.927	0.054
Genomic superior_thalamic_radiation	-0.014	0.012	-1.202	0.229
Genomic uncinate_fasciculus	-0.032	0.011	-2.957	0.003
Genomic forceps_major	-0.031	0.012	-2.589	0.010
Genomic forceps_minor	-0.031	0.012	-2.573	0.010
Genomic middle_cerebellar_peduncle	-0.020	0.012	-1.585	0.113

Table S7. The effect of unpruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on tract categories (FA) (N = 6,401).

PGRS THRESHOLD: 0.01	Value	Std. Error	t-value	p-value
NETRIN1 gFA	-0.025	0.012	-2.065	0.039
NETRIN1 Association fibres	-0.024	0.012	-2.024	0.043
NETRIN1 Thalamic radiations	-0.020	0.012	-1.615	0.106
NETRIN1 Projection fibres	-0.024	0.012	-1.963	0.050
Genomic gFA	-0.029	0.012	-2.431	0.015
Genomic Association fibres	-0.031	0.012	-2.574	0.010
Genomic Thalamic radiations	-0.020	0.012	-1.685	0.092
Genomic Projection fibres	-0.021	0.012	-1.716	0.086
PGRS THRESHOLD: 0.05				
NETRIN1 gFA	-0.012	0.012	-1.030	0.303
NETRIN1 Association fibres	-0.016	0.012	-1.333	0.183
NETRIN1 Thalamic radiations	-0.007	0.012	-0.590	0.555
NETRIN1 Projection fibres	-0.007	0.012	-0.552	0.581
Genomic gFA	-0.033	0.012	-2.776	0.006
Genomic Association fibres	-0.034	0.012	-2.845	0.004
Genomic Thalamic radiations	-0.026	0.012	-2.128	0.033
Genomic Projection fibres	-0.025	0.012	-2.073	0.038
PGRS THRESHOLD: 0.1				
NETRIN1 gFA	-0.018	0.012	-1.494	0.135
NETRIN1 Association fibres	-0.020	0.012	-1.684	0.092
NETRIN1 Thalamic radiations	-0.014	0.012	-1.125	0.261
NETRIN1 Projection fibres	-0.012	0.012	-1.032	0.302
Genomic gFA	-0.032	0.012	-2.656	0.008
Genomic Association fibres	-0.032	0.012	-2.728	0.006
Genomic Thalamic radiations	-0.022	0.012	-1.820	0.069
Genomic Projection fibres	-0.026	0.012	-2.201	0.028
PGRS THRESHOLD: 1				
NETRIN1 gFA	-0.027	0.012	-2.288	0.022
NETRIN1 Association fibres	-0.034	0.012	-2.903	0.004
NETRIN1 Thalamic radiations	-0.019	0.012	-1.590	0.112
NETRIN1 Projection fibres	-0.011	0.012	-0.881	0.379
Genomic gFA	-0.034	0.012	-2.824	0.005
Genomic Association fibres	-0.035	0.012	-2.927	0.003
Genomic Thalamic radiations	-0.023	0.012	-1.863	0.062
Genomic Projection fibres	-0.029	0.012	-2.443	0.015

Table S8. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on individual white matter tracts (FA) (N = 6,420).

PGRS THRESHOLD: 0.5	Value	Std. Error	t-value	p-value
NETRIN1 acoustic_radiation	0.002	0.011	0.222	0.824
NETRIN1 anterior_thalamic_radiation	-0.021	0.012	-1.800	0.072
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.024	0.011	-2.199	0.028
NETRIN1 parahippocampal_part_of_cingulum	-0.008	0.011	-0.731	0.465
NETRIN1 corticospinal_tract	0.001	0.011	0.125	0.900
NETRIN1 inferior_fronto_occipital_fasciculus	-0.022	0.012	-1.899	0.058
NETRIN1 inferior_longitudinal_fasciculus	-0.021	0.012	-1.853	0.064
NETRIN1 medial_lemniscus	-0.009	0.010	-0.826	0.409
NETRIN1 posterior_thalamic_radiation	-0.013	0.011	-1.162	0.245
NETRIN1 superior_longitudinal_fasciculus	-0.034	0.012	-2.897	0.004
NETRIN1 superior_thalamic_radiation	-0.006	0.012	-0.466	0.641
NETRIN1 uncinate_fasciculus	-0.019	0.011	-1.698	0.090
NETRIN1 forceps_major	-0.014	0.012	-1.197	0.231
NETRIN1 forceps_minor	-0.018	0.012	-1.489	0.136
NETRIN1 middle_cerebellar_peduncle	-0.016	0.012	-1.270	0.204
Genomic acoustic_radiation	-0.016	0.011	-1.464	0.143
Genomic anterior_thalamic_radiation	-0.018	0.012	-1.530	0.126
Genomic cingulate_gyrus_part_of_cingulum	-0.020	0.011	-1.859	0.063
Genomic parahippocampal_part_of_cingulum	-0.022	0.011	-2.042	0.041
Genomic corticospinal_tract	-0.022	0.012	-1.878	0.060
Genomic inferior_fronto_occipital_fasciculus	-0.030	0.012	-2.579	0.010
Genomic inferior_longitudinal_fasciculus	-0.026	0.012	-2.258	0.024
Genomic medial_lemniscus	-0.006	0.011	-0.580	0.562
Genomic posterior_thalamic_radiation	-0.025	0.011	-2.224	0.026
Genomic superior_longitudinal_fasciculus	-0.025	0.012	-2.095	0.036
Genomic superior_thalamic_radiation	-0.018	0.012	-1.487	0.137
Genomic uncinate_fasciculus	-0.034	0.011	-3.111	0.002
Genomic forceps_major	-0.034	0.012	-2.781	0.005
Genomic forceps_minor	-0.033	0.012	-2.717	0.007
Genomic middle_cerebellar_peduncle	-0.023	0.012	-1.828	0.068

Table S9. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on tract categories (FA) (N = 6,420).

PGRS THRESHOLD: 0.5	Value	Std. Error	t-value	p-value
NETRIN1 gFA	-0.002	0.001	-2.197	0.028
NETRIN1 Association fibres	-0.002	0.001	-2.762	0.006
NETRIN1 Thalamic radiations	-0.001	0.000	-1.482	0.138
NETRIN1 Projection fibres	0.000	0.001	-0.904	0.366
Genomic gFA	-0.002	0.001	-2.769	0.006
Genomic Association fibres	-0.002	0.001	-2.836	0.005
Genomic Thalamic radiations	-0.001	0.000	-1.855	0.064
Genomic Projection fibres	-0.001	0.001	-2.415	0.016

Table S10. The effect of unpruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on individual white matter tracts (MD) (N = 6,390).

	Value	Std. Error	t-value	p-value
PGRS THRESHOLD: 0.01				
NETRIN1 acoustic_radiation	0.008	0.011	0.772	0.440
NETRIN1 anterior_thalamic_radiation	0.018	0.011	1.694	0.090
NETRIN1 cingulate_gyrus_part_of_cingulum	0.013	0.011	1.257	0.209
NETRIN1 parahippocampal_part_of_cingulum	-0.007	0.011	-0.621	0.535
NETRIN1 corticospinal_tract	0.003	0.011	0.270	0.787
NETRIN1 inferior_fronto_occipital_fasciculus	0.021	0.011	1.905	0.057
NETRIN1 inferior_longitudinal_fasciculus	0.019	0.011	1.727	0.084
NETRIN1 medial_lemniscus	0.007	0.011	0.659	0.510
NETRIN1 posterior_thalamic_radiation	0.016	0.011	1.466	0.143
NETRIN1 superior_longitudinal_fasciculus	0.023	0.011	2.046	0.041
NETRIN1 superior_thalamic_radiation	0.016	0.010	1.589	0.112
NETRIN1 uncinate_fasciculus	0.011	0.010	1.033	0.302
NETRIN1 bl.MD.wm.forceps_major	0.013	0.012	1.083	0.279
NETRIN1 bl.MD.wm.forceps_minor	0.022	0.012	1.946	0.052
NETRIN1 bl.MD.wm.middle_cerebellar_peduncle	0.003	0.012	0.239	0.811
Genomic acoustic_radiation	0.015	0.011	1.453	0.146
Genomic anterior_thalamic_radiation	0.020	0.011	1.878	0.060
Genomic cingulate_gyrus_part_of_cingulum	0.038	0.011	3.529	0.000
Genomic parahippocampal_part_of_cingulum	0.030	0.011	2.846	0.004
Genomic corticospinal_tract	0.030	0.011	2.654	0.008
Genomic inferior_fronto_occipital_fasciculus	0.032	0.011	2.879	0.004
Genomic inferior_longitudinal_fasciculus	0.029	0.011	2.618	0.009
Genomic medial_lemniscus	0.012	0.011	1.145	0.252
Genomic posterior_thalamic_radiation	0.016	0.011	1.493	0.135
Genomic superior_longitudinal_fasciculus	0.028	0.011	2.490	0.013
Genomic superior_thalamic_radiation	0.023	0.010	2.320	0.020
Genomic uncinate_fasciculus	0.033	0.010	3.148	0.002
Genomic bl.MD.wm.forceps_major	0.033	0.012	2.733	0.006
Genomic bl.MD.wm.forceps_minor	0.020	0.012	1.692	0.091
Genomic bl.MD.wm.middle_cerebellar_peduncle	0.004	0.012	0.362	0.718

	Value	Std. Error	t-value	p-value
PGRS THRESHOLD: 0.05				
NETRIN1 acoustic_radiation	-0.006	0.010	-0.561	0.575
NETRIN1 anterior_thalamic_radiation	0.015	0.011	1.426	0.154
NETRIN1 cingulate_gyrus_part_of_cingulum	0.014	0.011	1.354	0.176
NETRIN1 parahippocampal_part_of_cingulum	0.004	0.011	0.347	0.729
NETRIN1 corticospinal_tract	-0.003	0.011	-0.226	0.821
NETRIN1 inferior_fronto_occipital_fasciculus	0.015	0.011	1.303	0.193
NETRIN1 inferior_longitudinal_fasciculus	0.017	0.011	1.538	0.124
NETRIN1 medial_lemniscus	0.002	0.011	0.160	0.873
NETRIN1 posterior_thalamic_radiation	0.016	0.011	1.509	0.131
NETRIN1 superior_longitudinal_fasciculus	0.023	0.011	1.998	0.046
NETRIN1 superior_thalamic_radiation	0.014	0.010	1.420	0.156
NETRIN1 uncinate_fasciculus	0.008	0.010	0.752	0.452
NETRIN1 bl.MD.wm.forceps_major	0.014	0.012	1.172	0.241
NETRIN1 bl.MD.wm.forceps_minor	0.015	0.012	1.292	0.196
NETRIN1 bl.MD.wm.middle_cerebellar_peduncle	-0.002	0.012	-0.138	0.890
Genomic acoustic_radiation	0.021	0.011	1.959	0.050
Genomic anterior_thalamic_radiation	0.025	0.011	2.359	0.018
Genomic cingulate_gyrus_part_of_cingulum	0.040	0.011	3.734	0.000
Genomic parahippocampal_part_of_cingulum	0.033	0.011	3.108	0.002
Genomic corticospinal_tract	0.034	0.011	2.999	0.003
Genomic inferior_fronto_occipital_fasciculus	0.037	0.011	3.327	0.001
Genomic inferior_longitudinal_fasciculus	0.032	0.011	2.890	0.004
Genomic medial_lemniscus	0.012	0.011	1.091	0.275
Genomic posterior_thalamic_radiation	0.016	0.011	1.527	0.127
Genomic superior_longitudinal_fasciculus	0.032	0.011	2.819	0.005
Genomic superior_thalamic_radiation	0.028	0.010	2.812	0.005
Genomic uncinate_fasciculus	0.032	0.010	3.116	0.002
Genomic bl.MD.wm.forceps_major	0.032	0.012	2.663	0.008
Genomic bl.MD.wm.forceps_minor	0.024	0.012	2.103	0.036
Genomic bl.MD.wm.middle_cerebellar_peduncle	0.006	0.012	0.515	0.607
PGRS THRESHOLD: 0.1				
NETRIN1 acoustic_radiation	-0.005	0.010	-0.458	0.647
NETRIN1 anterior_thalamic_radiation	0.020	0.011	1.868	0.062
NETRIN1 cingulate_gyrus_part_of_cingulum	0.014	0.011	1.334	0.182
NETRIN1 parahippocampal_part_of_cingulum	-0.007	0.011	-0.710	0.478
NETRIN1 corticospinal_tract	0.002	0.011	0.204	0.838
NETRIN1 inferior_fronto_occipital_fasciculus	0.020	0.011	1.800	0.072
NETRIN1 inferior_longitudinal_fasciculus	0.020	0.011	1.832	0.067
NETRIN1 medial_lemniscus	0.011	0.011	1.018	0.309
NETRIN1 posterior_thalamic_radiation	0.018	0.011	1.638	0.102
NETRIN1 superior_longitudinal_fasciculus	0.030	0.011	2.611	0.009
NETRIN1 superior_thalamic_radiation	0.021	0.010	2.073	0.038
NETRIN1 uncinate_fasciculus	0.009	0.010	0.879	0.379
NETRIN1 forceps_major	0.017	0.012	1.407	0.159
NETRIN1 forceps_minor	0.018	0.012	1.597	0.110
NETRIN1 middle_cerebellar_peduncle	0.004	0.012	0.298	0.766

	Value	Std. Error	t-value	p-value
Genomic acoustic_radiation	0.022	0.011	2.107	0.035
Genomic anterior_thalamic_radiation	0.023	0.011	2.143	0.032
Genomic cingulate_gyrus_part_of_cingulum	0.038	0.011	3.601	0.000
Genomic parahippocampal_part_of_cingulum	0.033	0.011	3.098	0.002
Genomic corticospinal_tract	0.032	0.011	2.802	0.005
Genomic inferior_fronto_occipital_fasciculus	0.034	0.011	3.081	0.002
Genomic inferior_longitudinal_fasciculus	0.030	0.011	2.689	0.007
Genomic medial_lemniscus	0.005	0.011	0.489	0.625
Genomic posterior_thalamic_radiation	0.009	0.011	0.884	0.377
Genomic superior_longitudinal_fasciculus	0.030	0.011	2.617	0.009
Genomic superior_thalamic_radiation	0.024	0.010	2.442	0.015
Genomic uncinate_fasciculus	0.034	0.010	3.320	0.001
Genomic forceps_major	0.028	0.012	2.358	0.018
Genomic forceps_minor	0.021	0.012	1.783	0.075
Genomic middle_cerebellar_peduncle	0.008	0.012	0.666	0.505
PGRS THRESHOLD: 1				
NETRIN1 acoustic_radiation	0.004	0.010	0.347	0.729
NETRIN1 anterior_thalamic_radiation	0.028	0.011	2.669	0.008
NETRIN1 cingulate_gyrus_part_of_cingulum	0.022	0.011	2.023	0.043
NETRIN1 parahippocampal_part_of_cingulum	0.000	0.011	-0.023	0.981
NETRIN1 corticospinal_tract	0.017	0.011	1.525	0.127
NETRIN1 inferior_fronto_occipital_fasciculus	0.028	0.011	2.551	0.011
NETRIN1 inferior_longitudinal_fasciculus	0.029	0.011	2.553	0.011
NETRIN1 medial_lemniscus	0.005	0.011	0.428	0.669
NETRIN1 posterior_thalamic_radiation	0.026	0.011	2.453	0.014
NETRIN1 superior_longitudinal_fasciculus	0.033	0.011	2.953	0.003
NETRIN1 superior_thalamic_radiation	0.027	0.010	2.763	0.006
NETRIN1 uncinate_fasciculus	0.020	0.010	1.900	0.058
NETRIN1 forceps_major	0.018	0.012	1.519	0.129
NETRIN1 forceps_minor	0.021	0.012	1.791	0.073
NETRIN1 middle_cerebellar_peduncle	0.011	0.012	0.890	0.373
Genomic acoustic_radiation	0.019	0.011	1.841	0.066
Genomic anterior_thalamic_radiation	0.021	0.011	2.021	0.043
Genomic cingulate_gyrus_part_of_cingulum	0.036	0.011	3.332	0.001
Genomic parahippocampal_part_of_cingulum	0.034	0.011	3.223	0.001
Genomic corticospinal_tract	0.023	0.011	1.997	0.046
Genomic inferior_fronto_occipital_fasciculus	0.032	0.011	2.828	0.005
Genomic inferior_longitudinal_fasciculus	0.025	0.011	2.262	0.024
Genomic medial_lemniscus	0.005	0.011	0.470	0.639
Genomic posterior_thalamic_radiation	0.002	0.011	0.142	0.887
Genomic superior_longitudinal_fasciculus	0.024	0.011	2.156	0.031
Genomic superior_thalamic_radiation	0.018	0.010	1.804	0.071
Genomic uncinate_fasciculus	0.030	0.010	2.844	0.004
Genomic forceps_major	0.029	0.012	2.447	0.014
Genomic forceps_minor	0.021	0.012	1.858	0.063
Genomic middle_cerebellar_peduncle	0.012	0.012	0.965	0.335

Table S11. The effect of unpruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on tract categories (MD) (N = 6,390).

	Value	Std. Error	t-value	p-value
PGRS THRESHOLD: 0.01				
NETRIN1 gMD	0.018	0.012	1.574	0.116
NETRIN1 Association fibres	0.013	0.012	1.086	0.277
NETRIN1 Thalamic radiations	0.019	0.011	1.781	0.075
NETRIN1 Projection fibres	0.013	0.012	1.087	0.277
Genomic gMD	0.037	0.012	3.248	0.001
Genomic Association fibres	0.043	0.012	3.707	0.000
Genomic Thalamic radiations	0.022	0.011	2.027	0.043
Genomic Projection fibres	0.026	0.012	2.180	0.029
PGRS THRESHOLD: 0.05				
NETRIN1 gMD	0.016	0.011	1.380	0.168
NETRIN1 Association fibres	0.015	0.012	1.320	0.187
NETRIN1 Thalamic radiations	0.018	0.011	1.669	0.095
NETRIN1 Projection fibres	0.004	0.012	0.322	0.748
Genomic gMD	0.041	0.011	3.607	0.000
Genomic Association fibres	0.047	0.012	4.033	0.000
Genomic Thalamic radiations	0.025	0.011	2.334	0.020
Genomic Projection fibres	0.030	0.012	2.478	0.013
PGRS THRESHOLD: 0.1				
NETRIN1 gMD	0.018	0.011	1.596	0.111
NETRIN1 Association fibres	0.013	0.012	1.106	0.269
NETRIN1 Thalamic radiations	0.022	0.011	2.055	0.040
NETRIN1 Projection fibres	0.011	0.012	0.920	0.358
Genomic gMD	0.038	0.011	3.342	0.001
Genomic Association fibres	0.046	0.012	3.934	0.000
Genomic Thalamic radiations	0.020	0.011	1.822	0.069
Genomic Projection fibres	0.029	0.012	2.391	0.017
PGRS THRESHOLD: 1				
NETRIN1 gMD	0.029	0.011	2.524	0.012
NETRIN1 Association fibres	0.023	0.012	2.014	0.044
NETRIN1 Thalamic radiations	0.031	0.011	2.944	0.003
NETRIN1 Projection fibres	0.020	0.012	1.686	0.092
Genomic gMD	0.034	0.011	2.974	0.003
Genomic Association fibres	0.043	0.012	3.666	0.000
Genomic Thalamic radiations	0.013	0.011	1.229	0.219
Genomic Projection fibres	0.030	0.012	2.494	0.013

Table S12. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on tract categories (MD) (N = 6,420).

PGRS THRESHOLD: 0.5	Value	Std. Error	t-value	p-value
NETRIN1 acoustic_radiation	0.005	0.011	0.484	0.628
NETRIN1 anterior_thalamic_radiation	0.023	0.011	2.171	0.030
NETRIN1 cingulate_gyrus_part_of_cingulum	0.019	0.011	1.682	0.093
NETRIN1 parahippocampal_part_of_cingulum	0.000	0.011	-0.004	0.997
NETRIN1 corticospinal_tract	0.014	0.012	1.232	0.218
NETRIN1 inferior_fronto_occipital_fasciculus	0.025	0.011	2.242	0.025
NETRIN1 inferior_longitudinal_fasciculus	0.027	0.011	2.377	0.017
NETRIN1 medial_lemniscus	0.003	0.011	0.288	0.774
NETRIN1 posterior_thalamic_radiation	0.024	0.011	2.213	0.027
NETRIN1 superior_longitudinal_fasciculus	0.030	0.011	2.649	0.008
NETRIN1 superior_thalamic_radiation	0.024	0.010	2.345	0.019
NETRIN1 uncinate_fasciculus	0.017	0.011	1.559	0.119
NETRIN1 forceps_major	0.019	0.012	1.599	0.110
NETRIN1 forceps_minor	0.019	0.012	1.592	0.111
NETRIN1 middle_cerebellar_peduncle	0.012	0.012	0.984	0.325
Genomic acoustic_radiation	0.010	0.011	0.949	0.342
Genomic anterior_thalamic_radiation	0.011	0.011	1.009	0.313
Genomic cingulate_gyrus_part_of_cingulum	0.021	0.011	1.852	0.064
Genomic parahippocampal_part_of_cingulum	0.027	0.011	2.485	0.013
Genomic corticospinal_tract	0.009	0.012	0.800	0.424
Genomic inferior_fronto_occipital_fasciculus	0.019	0.011	1.630	0.103
Genomic inferior_longitudinal_fasciculus	0.013	0.011	1.138	0.255
Genomic medial_lemniscus	-0.004	0.011	-0.378	0.705
Genomic posterior_thalamic_radiation	-0.006	0.011	-0.505	0.613
Genomic superior_longitudinal_fasciculus	0.013	0.012	1.113	0.266
Genomic superior_thalamic_radiation	0.007	0.011	0.653	0.514
Genomic uncinate_fasciculus	0.017	0.011	1.588	0.112
Genomic forceps_major	0.020	0.012	1.624	0.104
Genomic forceps_minor	0.012	0.012	0.982	0.326
Genomic middle_cerebellar_peduncle	0.005	0.012	0.437	0.662

Table S13. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on tract categories (MD) (N = 6,320).

PGRS THRESHOLD: 0.5	Value	Std. Error	t-value	p-value
NETRIN1 gMD	3.4E-06	1.4E-06	2.4E+00	1.6E-02
NETRIN1 Association fibres	2.0E-06	1.1E-06	1.9E+00	5.8E-02
NETRIN1 Thalamic radiations	2.2E-06	7.9E-07	2.8E+00	5.4E-03
NETRIN1 Projection fibres	1.4E-06	8.0E-07	1.8E+00	7.7E-02
Genomic gMD	4.2E-06	1.4E-06	2.9E+00	3.5E-03
Genomic Association fibres	3.9E-06	1.1E-06	3.6E+00	3.3E-04
Genomic Thalamic radiations	9.8E-07	7.9E-07	1.2E+00	2.2E-01
Genomic Projection fibres	1.9E-06	8.1E-07	2.4E+00	1.7E-02

Table S14. The effect of pruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on individual white matter tracts (FA) (N = 6,401).

Pruned NETRIN1- and Genomic-PRS with outliers included (6,420) and outliers excluded (6,401 for FA and 6,390 for MD) at all 5 thresholds (0.01, 0.05, 0.1, 0.5, 1)

	Value	Std. Error	t-value	p-value
PGRS THRESHOLD: 0.01				
NETRIN1 acoustic_radiation	-0.004	0.011	-0.349	0.727
NETRIN1 anterior_thalamic_radiation	-0.020	0.011	-1.709	0.087
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.008	0.011	-0.704	0.482
NETRIN1 parahippocampal_part_of_cingulum	-0.007	0.011	-0.641	0.521
NETRIN1 corticospinal_tract	-0.022	0.011	-1.923	0.055
NETRIN1 inferior_fronto_occipital_fasciculus	-0.024	0.012	-2.058	0.040
NETRIN1 inferior_longitudinal_fasciculus	-0.024	0.012	-2.047	0.041
NETRIN1 medial_lemniscus	-0.012	0.010	-1.131	0.258
NETRIN1 posterior_thalamic_radiation	-0.014	0.011	-1.238	0.216
NETRIN1 superior_longitudinal_fasciculus	-0.028	0.012	-2.408	0.016
NETRIN1 superior_thalamic_radiation	-0.020	0.012	-1.677	0.094
NETRIN1 uncinate_fasciculus	-0.023	0.011	-2.156	0.031
NETRIN1 bl.FA.wm.forceps_major	-0.014	0.012	-1.137	0.255
NETRIN1 bl.FA.wm.forceps_minor	-0.009	0.012	-0.784	0.433
NETRIN1 bl.FA.wm.middle_cerebellar_peduncle	-0.028	0.012	-2.257	0.024
Genomic acoustic_radiation	-0.010	0.011	-0.942	0.346
Genomic anterior_thalamic_radiation	-0.017	0.011	-1.440	0.150
Genomic cingulate_gyrus_part_of_cingulum	-0.008	0.011	-0.785	0.432
Genomic parahippocampal_part_of_cingulum	0.009	0.011	0.810	0.418
Genomic corticospinal_tract	-0.010	0.011	-0.889	0.374
Genomic inferior_fronto_occipital_fasciculus	-0.014	0.012	-1.249	0.212
Genomic inferior_longitudinal_fasciculus	-0.012	0.012	-1.023	0.306
Genomic medial_lemniscus	0.000	0.010	0.010	0.992
Genomic posterior_thalamic_radiation	-0.011	0.011	-0.965	0.335
Genomic superior_longitudinal_fasciculus	-0.013	0.012	-1.080	0.280
Genomic superior_thalamic_radiation	-0.016	0.012	-1.332	0.183
Genomic uncinate_fasciculus	-0.019	0.011	-1.793	0.073
Genomic bl.FA.wm.forceps_major	-0.013	0.012	-1.086	0.278
Genomic bl.FA.wm.forceps_minor	-0.018	0.012	-1.475	0.140
Genomic bl.FA.wm.middle_cerebellar_peduncle	0.017	0.012	1.369	0.171
PGRS THRESHOLD: 0.05				
NETRIN1 acoustic_radiation	0.008	0.011	0.770	0.441
NETRIN1 anterior_thalamic_radiation	-0.012	0.011	-1.047	0.295
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.007	0.011	-0.627	0.531
NETRIN1 parahippocampal_part_of_cingulum	-0.014	0.011	-1.335	0.182
NETRIN1 corticospinal_tract	-0.002	0.011	-0.146	0.884
NETRIN1 inferior_fronto_occipital_fasciculus	-0.007	0.011	-0.590	0.555

	Value	Std. Error	t-value	p-value
NETRIN1 inferior_longitudinal_fasciculus	-0.010	0.011	-0.865	0.387
NETRIN1 medial_lemniscus	-0.006	0.010	-0.574	0.566
NETRIN1 posterior_thalamic_radiation	-0.003	0.011	-0.304	0.761
NETRIN1 superior_longitudinal_fasciculus	-0.015	0.012	-1.290	0.197
NETRIN1 superior_thalamic_radiation	-0.003	0.012	-0.275	0.783
NETRIN1 uncinata_fasciculus	-0.011	0.011	-1.030	0.303
NETRIN1 bl.FA.wm.forceps_major	-0.004	0.012	-0.292	0.770
NETRIN1 bl.FA.wm.forceps_minor	-0.002	0.012	-0.178	0.858
NETRIN1 bl.FA.wm.middle_cerebellar_peduncle	-0.015	0.012	-1.200	0.230
Genomic acoustic_radiation	-0.005	0.011	-0.462	0.644
Genomic anterior_thalamic_radiation	-0.010	0.011	-0.901	0.367
Genomic cingulate_gyrus_part_of_cingulum	-0.004	0.011	-0.350	0.726
Genomic parahippocampal_part_of_cingulum	0.001	0.011	0.103	0.918
Genomic corticospinal_tract	-0.014	0.011	-1.272	0.203
Genomic inferior_fronto_occipital_fasciculus	-0.016	0.011	-1.351	0.177
Genomic inferior_longitudinal_fasciculus	-0.015	0.011	-1.281	0.200
Genomic medial_lemniscus	-0.006	0.010	-0.569	0.569
Genomic posterior_thalamic_radiation	-0.019	0.011	-1.716	0.086
Genomic superior_longitudinal_fasciculus	-0.012	0.012	-1.076	0.282
Genomic superior_thalamic_radiation	-0.019	0.012	-1.596	0.110
Genomic uncinata_fasciculus	-0.017	0.011	-1.557	0.119
Genomic bl.FA.wm.forceps_major	-0.013	0.012	-1.093	0.275
Genomic bl.FA.wm.forceps_minor	-0.014	0.012	-1.186	0.236
Genomic bl.FA.wm.middle_cerebellar_peduncle	-0.003	0.012	-0.271	0.786
PGRS THRESHOLD: 0.1				
NETRIN1 acoustic_radiation	0.005	0.011	0.452	0.652
NETRIN1 anterior_thalamic_radiation	-0.017	0.011	-1.442	0.149
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.013	0.011	-1.238	0.216
NETRIN1 parahippocampal_part_of_cingulum	-0.007	0.011	-0.681	0.496
NETRIN1 corticospinal_tract	-0.003	0.011	-0.225	0.822
NETRIN1 inferior_fronto_occipital_fasciculus	-0.016	0.012	-1.381	0.167
NETRIN1 inferior_longitudinal_fasciculus	-0.014	0.012	-1.221	0.222
NETRIN1 medial_lemniscus	-0.018	0.010	-1.730	0.084
NETRIN1 posterior_thalamic_radiation	-0.007	0.011	-0.601	0.548
NETRIN1 superior_longitudinal_fasciculus	-0.026	0.012	-2.205	0.027
NETRIN1 superior_thalamic_radiation	-0.010	0.012	-0.871	0.384
NETRIN1 uncinata_fasciculus	-0.010	0.011	-0.896	0.370
NETRIN1 forceps_major	-0.012	0.012	-1.004	0.316
NETRIN1 forceps_minor	-0.013	0.012	-1.041	0.298
NETRIN1 middle_cerebellar_peduncle	-0.011	0.012	-0.922	0.356
Genomic acoustic_radiation	0.001	0.011	0.080	0.936
Genomic anterior_thalamic_radiation	0.002	0.011	0.146	0.884
Genomic cingulate_gyrus_part_of_cingulum	-0.001	0.011	-0.075	0.940
Genomic parahippocampal_part_of_cingulum	-0.002	0.011	-0.188	0.851
Genomic corticospinal_tract	-0.015	0.011	-1.345	0.179

	Value	Std. Error	t-value	p-value
Genomic inferior_fronto_occipital_fasciculus	-0.008	0.011	-0.723	0.469
Genomic inferior_longitudinal_fasciculus	-0.009	0.012	-0.760	0.447
Genomic medial_lemniscus	-0.001	0.010	-0.131	0.896
Genomic posterior_thalamic_radiation	-0.009	0.011	-0.770	0.441
Genomic superior_longitudinal_fasciculus	-0.007	0.012	-0.580	0.562
Genomic superior_thalamic_radiation	-0.011	0.012	-0.951	0.342
Genomic uncinate_fasciculus	-0.017	0.011	-1.572	0.116
Genomic forceps_major	-0.008	0.012	-0.632	0.528
Genomic forceps_minor	-0.006	0.012	-0.518	0.605
Genomic middle_cerebellar_peduncle	-0.016	0.012	-1.281	0.200
PGRS THRESHOLD: 0.5				
NETRIN1 acoustic_radiation	0.006	0.011	0.520	0.603
NETRIN1 anterior_thalamic_radiation	-0.021	0.011	-1.811	0.070
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.023	0.011	-2.201	0.028
NETRIN1 parahippocampal_part_of_cingulum	-0.006	0.011	-0.583	0.560
NETRIN1 corticospinal_tract	0.002	0.011	0.204	0.839
NETRIN1 inferior_fronto_occipital_fasciculus	-0.021	0.011	-1.824	0.068
NETRIN1 inferior_longitudinal_fasciculus	-0.021	0.012	-1.790	0.074
NETRIN1 medial_lemniscus	-0.011	0.010	-1.061	0.289
NETRIN1 posterior_thalamic_radiation	-0.011	0.011	-0.981	0.327
NETRIN1 superior_longitudinal_fasciculus	-0.035	0.012	-3.031	0.002
NETRIN1 superior_thalamic_radiation	-0.006	0.012	-0.521	0.603
NETRIN1 uncinate_fasciculus	-0.018	0.011	-1.702	0.089
NETRIN1 forceps_major	-0.009	0.012	-0.740	0.459
NETRIN1 forceps_minor	-0.013	0.012	-1.071	0.284
NETRIN1 middle_cerebellar_peduncle	-0.017	0.012	-1.363	0.173
Genomic acoustic_radiation	-0.005	0.011	-0.488	0.625
Genomic anterior_thalamic_radiation	-0.007	0.011	-0.607	0.544
Genomic cingulate_gyrus_part_of_cingulum	-0.008	0.011	-0.780	0.435
Genomic parahippocampal_part_of_cingulum	-0.013	0.011	-1.189	0.235
Genomic corticospinal_tract	-0.022	0.011	-1.926	0.054
Genomic inferior_fronto_occipital_fasciculus	-0.018	0.011	-1.581	0.114
Genomic inferior_longitudinal_fasciculus	-0.014	0.012	-1.242	0.214
Genomic medial_lemniscus	-0.011	0.010	-1.055	0.291
Genomic posterior_thalamic_radiation	-0.015	0.011	-1.346	0.178
Genomic superior_longitudinal_fasciculus	-0.012	0.012	-1.014	0.311
Genomic superior_thalamic_radiation	-0.016	0.012	-1.381	0.167
Genomic uncinate_fasciculus	-0.023	0.011	-2.172	0.030
Genomic forceps_major	-0.015	0.012	-1.270	0.204
Genomic forceps_minor	-0.014	0.012	-1.184	0.237
Genomic middle_cerebellar_peduncle	-0.016	0.012	-1.334	0.182
PGRS THRESHOLD: 1				
NETRIN1 acoustic_radiation	0.006	0.011	0.554	0.579
NETRIN1 anterior_thalamic_radiation	-0.022	0.011	-1.896	0.058
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.026	0.011	-2.428	0.015

	Value	Std. Error	t-value	p-value
NETRIN1 parahippocampal_part_of_cingulum	-0.006	0.011	-0.558	0.577
NETRIN1 corticospinal_tract	-0.001	0.011	-0.057	0.954
NETRIN1 inferior_fronto_occipital_fasciculus	-0.020	0.011	-1.765	0.078
NETRIN1 inferior_longitudinal_fasciculus	-0.019	0.011	-1.629	0.103
NETRIN1 medial_lemniscus	-0.011	0.010	-1.020	0.308
NETRIN1 posterior_thalamic_radiation	-0.011	0.011	-0.991	0.322
NETRIN1 superior_longitudinal_fasciculus	-0.034	0.012	-2.959	0.003
NETRIN1 superior_thalamic_radiation	-0.007	0.012	-0.582	0.560
NETRIN1 uncinate_fasciculus	-0.018	0.011	-1.635	0.102
NETRIN1 forceps_major	-0.008	0.012	-0.678	0.497
NETRIN1 forceps_minor	-0.013	0.012	-1.116	0.264
NETRIN1 middle_cerebellar_peduncle	-0.015	0.012	-1.195	0.232
Genomic acoustic_radiation	-0.005	0.011	-0.502	0.616
Genomic anterior_thalamic_radiation	-0.009	0.011	-0.755	0.450
Genomic cingulate_gyrus_part_of_cingulum	-0.010	0.011	-0.976	0.329
Genomic parahippocampal_part_of_cingulum	-0.015	0.011	-1.373	0.170
Genomic corticospinal_tract	-0.021	0.011	-1.826	0.068
Genomic inferior_fronto_occipital_fasciculus	-0.018	0.011	-1.588	0.112
Genomic inferior_longitudinal_fasciculus	-0.014	0.011	-1.231	0.218
Genomic medial_lemniscus	-0.011	0.010	-1.044	0.296
Genomic posterior_thalamic_radiation	-0.013	0.011	-1.151	0.250
Genomic superior_longitudinal_fasciculus	-0.010	0.012	-0.848	0.396
Genomic superior_thalamic_radiation	-0.015	0.012	-1.263	0.207
Genomic uncinate_fasciculus	-0.024	0.011	-2.174	0.030
Genomic forceps_major	-0.014	0.012	-1.167	0.243
Genomic forceps_minor	-0.012	0.012	-1.017	0.309
Genomic middle_cerebellar_peduncle	-0.017	0.012	-1.344	0.179

Table S15. The effect of pruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on tract categories (FA) (N = 6,401).

PGRS THRESHOLD: 0.01	Value	Std. Error	t-value	p-value
NETRIN1 gFA	-0.026	0.012	-2.186	0.029
NETRIN1 Association fibres	-0.025	0.012	-2.066	0.039
NETRIN1 Thalamic radiations	-0.022	0.012	-1.853	0.064
NETRIN1 Projection fibres	-0.025	0.012	-2.098	0.036
Genomic gFA	-0.015	0.012	-1.226	0.220
Genomic Association fibres	-0.013	0.012	-1.068	0.285
Genomic Thalamic radiations	-0.018	0.012	-1.488	0.137
Genomic Projection fibres	-0.009	0.012	-0.766	0.444
PGRS THRESHOLD: 0.05	Value	Std. Error	t-value	p-value
NETRIN1 gFA	-0.011	0.012	-0.943	0.346
NETRIN1 Association fibres	-0.015	0.012	-1.245	0.213
NETRIN1 Thalamic radiations	-0.008	0.012	-0.635	0.526
NETRIN1 Projection fibres	-0.004	0.012	-0.367	0.714
Genomic gFA	-0.017	0.012	-1.385	0.166
Genomic Association fibres	-0.013	0.012	-1.074	0.283
Genomic Thalamic radiations	-0.021	0.012	-1.740	0.082
Genomic Projection fibres	-0.015	0.012	-1.283	0.200
PGRS THRESHOLD: 0.1	Value	Std. Error	t-value	p-value
NETRIN1 gFA	-0.018	0.012	-1.518	0.129
NETRIN1 Association fibres	-0.020	0.012	-1.720	0.085
NETRIN1 Thalamic radiations	-0.014	0.012	-1.147	0.251
NETRIN1 Projection fibres	-0.012	0.012	-0.981	0.327
Genomic gFA	-0.010	0.012	-0.855	0.393
Genomic Association fibres	-0.008	0.012	-0.714	0.476
Genomic Thalamic radiations	-0.008	0.012	-0.666	0.505
Genomic Projection fibres	-0.013	0.012	-1.105	0.269
PGRS THRESHOLD: 0.5	Value	Std. Error	t-value	p-value
NETRIN1 gFA	-0.023	0.012	-1.966	0.049
NETRIN1 Association fibres	-0.031	0.012	-2.567	0.010
NETRIN1 Thalamic radiations	-0.016	0.012	-1.327	0.184
NETRIN1 Projection fibres	-0.008	0.012	-0.668	0.504
Genomic gFA	-0.021	0.012	-1.794	0.073
Genomic Association fibres	-0.020	0.012	-1.656	0.098
Genomic Thalamic radiations	-0.017	0.012	-1.376	0.169
Genomic Projection fibres	-0.024	0.012	-1.983	0.047
PGRS THRESHOLD: 1	Value	Std. Error	t-value	p-value
NETRIN1 gFA	-0.024	0.012	-1.991	0.047
NETRIN1 Association fibres	-0.031	0.012	-2.585	0.010
NETRIN1 Thalamic radiations	-0.017	0.012	-1.387	0.166
NETRIN1 Projection fibres	-0.009	0.012	-0.715	0.475
Genomic gFA	-0.021	0.012	-1.793	0.073
Genomic Association fibres	-0.021	0.012	-1.741	0.082
Genomic Thalamic radiations	-0.016	0.012	-1.296	0.195
Genomic Projection fibres	-0.023	0.012	-1.899	0.058

Table S16. The effect of pruned NETRIN1- and Genomic-PRS at threshold 0.5 on individual white matter tracts (FA) (N = 6,420).

PGRS THRESHOLD: 0.5	Value	Std. Error	t-value	p-value
NETRIN1 acoustic_radiation	0.002	0.011	0.198	0.843
NETRIN1 anterior_thalamic_radiation	-0.022	0.012	-1.922	0.055
NETRIN1 cingulate_gyrus_part_of_cingulum	-0.024	0.011	-2.234	0.025
NETRIN1 parahippocampal_part_of_cingulum	-0.007	0.011	-0.644	0.520
NETRIN1 corticospinal_tract	-0.001	0.011	-0.100	0.920
NETRIN1 inferior_fronto_occipital_fasciculus	-0.023	0.012	-1.957	0.050
NETRIN1 inferior_longitudinal_fasciculus	-0.022	0.012	-1.865	0.062
NETRIN1 medial_lemniscus	-0.013	0.011	-1.240	0.215
NETRIN1 posterior_thalamic_radiation	-0.013	0.011	-1.120	0.263
NETRIN1 superior_longitudinal_fasciculus	-0.035	0.012	-3.029	0.002
NETRIN1 superior_thalamic_radiation	-0.008	0.012	-0.693	0.488
NETRIN1 uncinate_fasciculus	-0.020	0.011	-1.841	0.066
NETRIN1 forceps_major	-0.011	0.012	-0.908	0.364
NETRIN1 forceps_minor	-0.016	0.012	-1.299	0.194
NETRIN1 middle_cerebellar_peduncle	-0.017	0.012	-1.360	0.174
Genomic acoustic_radiation	-0.008	0.011	-0.773	0.439
Genomic anterior_thalamic_radiation	-0.010	0.012	-0.894	0.371
Genomic cingulate_gyrus_part_of_cingulum	-0.010	0.011	-0.925	0.355
Genomic parahippocampal_part_of_cingulum	-0.014	0.011	-1.309	0.191
Genomic corticospinal_tract	-0.025	0.012	-2.154	0.031
Genomic inferior_fronto_occipital_fasciculus	-0.021	0.012	-1.758	0.079
Genomic inferior_longitudinal_fasciculus	-0.017	0.012	-1.436	0.151
Genomic medial_lemniscus	-0.015	0.011	-1.382	0.167
Genomic posterior_thalamic_radiation	-0.018	0.011	-1.586	0.113
Genomic superior_longitudinal_fasciculus	-0.014	0.012	-1.193	0.233
Genomic superior_thalamic_radiation	-0.019	0.012	-1.613	0.107
Genomic uncinate_fasciculus	-0.025	0.011	-2.284	0.022
Genomic forceps_major	-0.019	0.012	-1.521	0.128
Genomic forceps_minor	-0.017	0.012	-1.370	0.171
Genomic middle_cerebellar_peduncle	-0.019	0.012	-1.545	0.122

Table S17. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on tract categories (FA) (N = 6,420).

PGRS THRESHOLD: 0.5	Value	Std. Error	t-value	p-value
NETRIN1 gFA	-0.002	0.001	-1.966	0.049
NETRIN1 Association fibres	-0.002	0.001	-2.567	0.010
NETRIN1 Thalamic radiations	-0.001	0.000	-1.327	0.184
NETRIN1 Projection fibres	0.000	0.001	-0.668	0.504
Genomic gFA	-0.002	0.001	-1.794	0.073
Genomic Association fibres	-0.001	0.001	-1.656	0.098
Genomic Thalamic radiations	-0.001	0.000	-1.376	0.169
Genomic Projection fibres	-0.001	0.001	-1.983	0.047

Table S18. The effect of pruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on individual white matter tracts (MD) (N = 6,390).

	Value	Std. Error	t-value	p-value
PGRS THRESHOLD: 0.01				
NETRIN1 acoustic_radiation	0.006	0.011	0.544	0.586
NETRIN1 anterior_thalamic_radiation	0.008	0.011	0.773	0.439
NETRIN1 cingulate_gyrus_part_of_cingulum	0.013	0.011	1.241	0.215
NETRIN1 parahippocampal_part_of_cingulum	-0.012	0.011	-1.116	0.264
NETRIN1 corticospinal_tract	-0.002	0.011	-0.206	0.837
NETRIN1 inferior_fronto_occipital_fasciculus	0.017	0.011	1.482	0.138
NETRIN1 inferior_longitudinal_fasciculus	0.017	0.011	1.543	0.123
NETRIN1 medial_lemniscus	0.013	0.011	1.225	0.220
NETRIN1 posterior_thalamic_radiation	0.008	0.011	0.773	0.439
NETRIN1 superior_longitudinal_fasciculus	0.018	0.011	1.556	0.120
NETRIN1 superior_thalamic_radiation	0.008	0.010	0.851	0.395
NETRIN1 uncinate_fasciculus	0.014	0.010	1.387	0.165
NETRIN1 bl.MD.wm.forceps_major	0.009	0.012	0.741	0.459
NETRIN1 bl.MD.wm.forceps_minor	0.016	0.012	1.390	0.165
NETRIN1 bl.MD.wm.middle_cerebellar_peduncle	-0.004	0.012	-0.350	0.726
Genomic acoustic_radiation	-0.004	0.011	-0.353	0.724
Genomic anterior_thalamic_radiation	0.019	0.011	1.833	0.067
Genomic cingulate_gyrus_part_of_cingulum	0.024	0.011	2.263	0.024
Genomic parahippocampal_part_of_cingulum	0.008	0.011	0.715	0.475
Genomic corticospinal_tract	0.012	0.011	1.041	0.298
Genomic inferior_fronto_occipital_fasciculus	0.019	0.011	1.711	0.087
Genomic inferior_longitudinal_fasciculus	0.008	0.011	0.758	0.449
Genomic medial_lemniscus	0.001	0.011	0.117	0.907
Genomic posterior_thalamic_radiation	-0.001	0.011	-0.100	0.920
Genomic superior_longitudinal_fasciculus	0.017	0.011	1.503	0.133
Genomic superior_thalamic_radiation	0.018	0.010	1.831	0.067
Genomic uncinate_fasciculus	0.023	0.010	2.213	0.027
Genomic bl.MD.wm.forceps_major	0.014	0.012	1.138	0.255
Genomic bl.MD.wm.forceps_minor	0.018	0.012	1.602	0.109
Genomic bl.MD.wm.middle_cerebellar_peduncle	0.010	0.012	0.821	0.411

	Value	Std. Error	t-value	p-value
PGRS THRESHOLD: 0.05				
NETRIN1 acoustic_radiation	-0.010	0.010	-0.947	0.344
NETRIN1 anterior_thalamic_radiation	0.006	0.011	0.571	0.568
NETRIN1 cingulate_gyrus_part_of_cingulum	0.014	0.011	1.273	0.203
NETRIN1 parahippocampal_part_of_cingulum	0.001	0.011	0.082	0.935
NETRIN1 corticospinal_tract	-0.006	0.011	-0.575	0.565
NETRIN1 inferior_fronto_occipital_fasciculus	0.010	0.011	0.883	0.377
NETRIN1 inferior_longitudinal_fasciculus	0.014	0.011	1.274	0.203
NETRIN1 medial_lemniscus	0.004	0.011	0.395	0.693
NETRIN1 posterior_thalamic_radiation	0.011	0.011	0.993	0.321
NETRIN1 superior_longitudinal_fasciculus	0.018	0.011	1.549	0.122
NETRIN1 superior_thalamic_radiation	0.007	0.010	0.741	0.458
NETRIN1 uncinate_fasciculus	0.008	0.010	0.780	0.435
NETRIN1 bl.MD.wm.forceps_major	0.011	0.012	0.937	0.349
NETRIN1 bl.MD.wm.forceps_minor	0.009	0.012	0.752	0.452
NETRIN1 bl.MD.wm.middle_cerebellar_peduncle	-0.007	0.012	-0.600	0.549
Genomic acoustic_radiation	0.004	0.010	0.428	0.669
Genomic anterior_thalamic_radiation	0.018	0.011	1.754	0.079
Genomic cingulate_gyrus_part_of_cingulum	0.021	0.011	1.993	0.046
Genomic parahippocampal_part_of_cingulum	0.013	0.011	1.222	0.222
Genomic corticospinal_tract	0.019	0.011	1.674	0.094
Genomic inferior_fronto_occipital_fasciculus	0.024	0.011	2.168	0.030
Genomic inferior_longitudinal_fasciculus	0.013	0.011	1.160	0.246
Genomic medial_lemniscus	0.008	0.011	0.724	0.469
Genomic posterior_thalamic_radiation	0.001	0.011	0.091	0.928
Genomic superior_longitudinal_fasciculus	0.017	0.011	1.492	0.136
Genomic superior_thalamic_radiation	0.017	0.010	1.735	0.083
Genomic uncinate_fasciculus	0.015	0.010	1.418	0.156
Genomic bl.MD.wm.forceps_major	0.016	0.012	1.298	0.194
Genomic bl.MD.wm.forceps_minor	0.020	0.012	1.703	0.089
Genomic bl.MD.wm.middle_cerebellar_peduncle	0.010	0.012	0.791	0.429
PGRS THRESHOLD: 0.1				
NETRIN1 acoustic_radiation	-0.008	0.011	-0.727	0.468
NETRIN1 anterior_thalamic_radiation	0.014	0.011	1.297	0.195
NETRIN1 cingulate_gyrus_part_of_cingulum	0.014	0.011	1.352	0.176
NETRIN1 parahippocampal_part_of_cingulum	-0.009	0.011	-0.899	0.369
NETRIN1 corticospinal_tract	-0.001	0.011	-0.071	0.943
NETRIN1 inferior_fronto_occipital_fasciculus	0.018	0.011	1.641	0.101
NETRIN1 inferior_longitudinal_fasciculus	0.020	0.011	1.774	0.076
NETRIN1 medial_lemniscus	0.015	0.011	1.377	0.169
NETRIN1 posterior_thalamic_radiation	0.014	0.011	1.334	0.182
NETRIN1 superior_longitudinal_fasciculus	0.027	0.011	2.413	0.016
NETRIN1 superior_thalamic_radiation	0.016	0.010	1.652	0.099
NETRIN1 uncinate_fasciculus	0.010	0.010	0.991	0.321
NETRIN1 forceps_major	0.014	0.012	1.205	0.228
NETRIN1 forceps_minor	0.015	0.012	1.284	0.199

	Value	Std. Error	t-value	p-value
NETRIN1 middle_cerebellar_peduncle	0.004	0.012	0.359	0.720
Genomic acoustic_radiation	0.002	0.011	0.161	0.872
Genomic anterior_thalamic_radiation	0.011	0.011	1.023	0.306
Genomic cingulate_gyrus_part_of_cingulum	0.014	0.011	1.306	0.191
Genomic parahippocampal_part_of_cingulum	0.016	0.011	1.537	0.124
Genomic corticospinal_tract	0.013	0.011	1.167	0.243
Genomic inferior_fronto_occipital_fasciculus	0.014	0.011	1.228	0.219
Genomic inferior_longitudinal_fasciculus	0.006	0.011	0.516	0.606
Genomic medial_lemniscus	-0.003	0.011	-0.323	0.747
Genomic posterior_thalamic_radiation	-0.008	0.011	-0.791	0.429
Genomic superior_longitudinal_fasciculus	0.009	0.011	0.832	0.405
Genomic superior_thalamic_radiation	0.008	0.010	0.776	0.438
Genomic uncinata_fasciculus	0.013	0.010	1.246	0.213
Genomic forceps_major	0.009	0.012	0.751	0.453
Genomic forceps_minor	0.010	0.012	0.852	0.394
Genomic middle_cerebellar_peduncle	0.009	0.012	0.712	0.476
PGRS THRESHOLD: 0.5				
NETRIN1 acoustic_radiation	-0.002	0.010	-0.187	0.852
NETRIN1 anterior_thalamic_radiation	0.020	0.011	1.854	0.064
NETRIN1 cingulate_gyrus_part_of_cingulum	0.017	0.011	1.586	0.113
NETRIN1 parahippocampal_part_of_cingulum	-0.009	0.011	-0.813	0.416
NETRIN1 corticospinal_tract	0.008	0.011	0.694	0.488
NETRIN1 inferior_fronto_occipital_fasciculus	0.025	0.011	2.193	0.028
NETRIN1 inferior_longitudinal_fasciculus	0.025	0.011	2.221	0.026
NETRIN1 medial_lemniscus	0.004	0.011	0.338	0.736
NETRIN1 posterior_thalamic_radiation	0.020	0.011	1.878	0.060
NETRIN1 superior_longitudinal_fasciculus	0.030	0.011	2.603	0.009
NETRIN1 superior_thalamic_radiation	0.020	0.010	2.051	0.040
NETRIN1 uncinata_fasciculus	0.015	0.010	1.421	0.155
NETRIN1 forceps_major	0.014	0.012	1.181	0.237
NETRIN1 forceps_minor	0.014	0.012	1.202	0.229
NETRIN1 middle_cerebellar_peduncle	0.009	0.012	0.759	0.448
Genomic acoustic_radiation	-0.002	0.010	-0.177	0.860
Genomic anterior_thalamic_radiation	0.013	0.011	1.216	0.224
Genomic cingulate_gyrus_part_of_cingulum	0.014	0.011	1.359	0.174
Genomic parahippocampal_part_of_cingulum	0.018	0.011	1.678	0.093
Genomic corticospinal_tract	0.002	0.011	0.205	0.838
Genomic inferior_fronto_occipital_fasciculus	0.014	0.011	1.238	0.216
Genomic inferior_longitudinal_fasciculus	0.006	0.011	0.495	0.621
Genomic medial_lemniscus	-0.002	0.011	-0.204	0.839
Genomic posterior_thalamic_radiation	-0.010	0.011	-0.972	0.331
Genomic superior_longitudinal_fasciculus	0.008	0.011	0.667	0.505
Genomic superior_thalamic_radiation	0.006	0.010	0.582	0.561
Genomic uncinata_fasciculus	0.010	0.010	0.960	0.337
Genomic forceps_major	0.014	0.012	1.202	0.230
Genomic forceps_minor	0.016	0.012	1.425	0.154
Genomic middle_cerebellar_peduncle	0.011	0.012	0.870	0.384

	Value	Std. Error	t-value	p-value
PGRS THRESHOLD: 1				
NETRIN1 acoustic_radiation	-0.003	0.010	-0.333	0.739
NETRIN1 anterior_thalamic_radiation	0.022	0.011	2.070	0.039
NETRIN1 cingulate_gyrus_part_of_cingulum	0.018	0.011	1.698	0.089
NETRIN1 parahippocampal_part_of_cingulum	-0.006	0.011	-0.608	0.543
NETRIN1 corticospinal_tract	0.009	0.011	0.789	0.430
NETRIN1 inferior_fronto_occipital_fasciculus	0.024	0.011	2.176	0.030
NETRIN1 inferior_longitudinal_fasciculus	0.023	0.011	2.018	0.044
NETRIN1 medial_lemniscus	0.004	0.011	0.355	0.723
NETRIN1 posterior_thalamic_radiation	0.020	0.011	1.875	0.061
NETRIN1 superior_longitudinal_fasciculus	0.029	0.011	2.576	0.010
NETRIN1 superior_thalamic_radiation	0.021	0.010	2.132	0.033
NETRIN1 uncinate_fasciculus	0.016	0.010	1.562	0.118
NETRIN1 forceps_major	0.013	0.012	1.067	0.286
NETRIN1 forceps_minor	0.016	0.012	1.403	0.161
NETRIN1 middle_cerebellar_peduncle	0.008	0.012	0.664	0.507
Genomic acoustic_radiation	-0.003	0.010	-0.318	0.750
Genomic anterior_thalamic_radiation	0.013	0.011	1.202	0.229
Genomic cingulate_gyrus_part_of_cingulum	0.014	0.011	1.292	0.196
Genomic parahippocampal_part_of_cingulum	0.019	0.011	1.780	0.075
Genomic corticospinal_tract	0.003	0.011	0.258	0.796
Genomic inferior_fronto_occipital_fasciculus	0.013	0.011	1.167	0.243
Genomic inferior_longitudinal_fasciculus	0.005	0.011	0.471	0.638
Genomic medial_lemniscus	-0.004	0.011	-0.396	0.692
Genomic posterior_thalamic_radiation	-0.013	0.011	-1.172	0.241
Genomic superior_longitudinal_fasciculus	0.006	0.011	0.549	0.583
Genomic superior_thalamic_radiation	0.005	0.010	0.464	0.643
Genomic uncinate_fasciculus	0.010	0.010	0.983	0.326
Genomic forceps_major	0.015	0.012	1.282	0.200
Genomic forceps_minor	0.012	0.012	1.044	0.296
Genomic middle_cerebellar_peduncle	0.012	0.012	1.006	0.314

Table S19. The effect of pruned NETRIN1- and Genomic-PRS at thresholds 0.01, 0.05, 0.1, 0.5 and 1 on tract categories (MD) (N = 6,390).

	Value	Std. Error	t-value	p-value
PGRS THRESHOLD: 0.01				
NETRIN1 gMD	0.011	0.012	0.998	0.318
NETRIN1 Association fibres	0.009	0.012	0.737	0.461
NETRIN1 Thalamic radiations	0.010	0.011	0.896	0.370
NETRIN1 Projection fibres	0.005	0.012	0.429	0.668
Genomic gMD	0.018	0.011	1.546	0.122
Genomic Association fibres	0.020	0.012	1.690	0.091
Genomic Thalamic radiations	0.011	0.011	1.041	0.298
Genomic Projection fibres	0.015	0.012	1.205	0.228
PGRS THRESHOLD: 0.05				
NETRIN1 gMD	0.010	0.011	0.844	0.399
NETRIN1 Association fibres	0.012	0.012	0.995	0.320
NETRIN1 Thalamic radiations	0.010	0.011	0.916	0.360
NETRIN1 Projection fibres	-0.003	0.012	-0.268	0.789
Genomic gMD	0.021	0.011	1.798	0.072
Genomic Association fibres	0.022	0.012	1.913	0.056
Genomic Thalamic radiations	0.012	0.011	1.091	0.276
Genomic Projection fibres	0.019	0.012	1.595	0.111
PGRS THRESHOLD: 0.1				
NETRIN1 gMD	0.015	0.011	1.327	0.184
NETRIN1 Association fibres	0.011	0.012	0.970	0.332
NETRIN1 Thalamic radiations	0.017	0.011	1.583	0.114
NETRIN1 Projection fibres	0.010	0.012	0.796	0.426
Genomic gMD	0.012	0.011	1.064	0.287
Genomic Association fibres	0.018	0.012	1.539	0.124
Genomic Thalamic radiations	0.001	0.011	0.120	0.904
Genomic Projection fibres	0.012	0.012	1.010	0.312
PGRS THRESHOLD: 0.5				
NETRIN1 gMD	0.020	0.011	1.783	0.075
NETRIN1 Association fibres	0.015	0.012	1.328	0.184
NETRIN1 Thalamic radiations	0.023	0.011	2.169	0.030
NETRIN1 Projection fibres	0.014	0.012	1.171	0.242
Genomic gMD	0.012	0.011	1.045	0.296
Genomic Association fibres	0.018	0.012	1.526	0.127
Genomic Thalamic radiations	0.001	0.011	0.050	0.960
Genomic Projection fibres	0.014	0.012	1.174	0.240
PGRS THRESHOLD: 1				
NETRIN1 gMD	0.021	0.011	1.829	0.068
NETRIN1 Association fibres	0.016	0.012	1.412	0.158
NETRIN1 Thalamic radiations	0.024	0.011	2.263	0.024
NETRIN1 Projection fibres	0.013	0.012	1.060	0.289
Genomic gMD	0.011	0.011	0.979	0.328
Genomic Association fibres	0.018	0.012	1.533	0.125
Genomic Thalamic radiations	-0.001	0.011	-0.091	0.928
Genomic Projection fibres	0.015	0.012	1.206	0.228

Table S20. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on individual white matter tracts (MD) (N = 6,420).

PGRS THRESHOLD: 0.5	Value	Std. Error	t-value	p-value
NETRIN1 acoustic_radiation	-0.002	0.011	-0.223	0.824
NETRIN1 anterior_thalamic_radiation	0.015	0.011	1.434	0.151
NETRIN1 cingulate_gyrus_part_of_cingulum	0.013	0.011	1.153	0.249
NETRIN1 parahippocampal_part_of_cingulum	-0.008	0.011	-0.762	0.446
NETRIN1 corticospinal_tract	0.004	0.012	0.341	0.733
NETRIN1 inferior_fronto_occipital_fasciculus	0.020	0.011	1.764	0.078
NETRIN1 inferior_longitudinal_fasciculus	0.020	0.011	1.779	0.075
NETRIN1 medial_lemniscus	0.001	0.011	0.059	0.953
NETRIN1 posterior_thalamic_radiation	0.017	0.011	1.588	0.112
NETRIN1 superior_longitudinal_fasciculus	0.023	0.011	2.036	0.042
NETRIN1 superior_thalamic_radiation	0.015	0.010	1.456	0.145
NETRIN1 uncinate_fasciculus	0.012	0.011	1.102	0.271
NETRIN1 forceps_major	0.014	0.012	1.146	0.252
NETRIN1 forceps_minor	0.011	0.012	0.949	0.342
NETRIN1 middle_cerebellar_peduncle	0.007	0.012	0.573	0.567
Genomic acoustic_radiation	-0.009	0.011	-0.817	0.414
Genomic anterior_thalamic_radiation	0.003	0.011	0.261	0.794
Genomic cingulate_gyrus_part_of_cingulum	0.003	0.011	0.234	0.815
Genomic parahippocampal_part_of_cingulum	0.010	0.011	0.980	0.327
Genomic corticospinal_tract	-0.008	0.012	-0.656	0.512
Genomic inferior_fronto_occipital_fasciculus	0.002	0.011	0.164	0.870
Genomic inferior_longitudinal_fasciculus	-0.005	0.011	-0.427	0.669
Genomic medial_lemniscus	-0.009	0.011	-0.790	0.430
Genomic posterior_thalamic_radiation	-0.018	0.011	-1.651	0.099
Genomic superior_longitudinal_fasciculus	-0.002	0.012	-0.187	0.851
Genomic superior_thalamic_radiation	-0.004	0.011	-0.335	0.738
Genomic uncinate_fasciculus	0.000	0.011	-0.035	0.972
Genomic forceps_major	0.005	0.012	0.440	0.660
Genomic forceps_minor	0.004	0.012	0.352	0.725
Genomic middle_cerebellar_peduncle	0.006	0.012	0.455	0.649

Table S21. The effect of unpruned NETRIN1- and Genomic-PRS at threshold 0.5 on tract categories (MD) (N = 6,420).

PGRS THRESHOLD: 0.5	Value	Std. Error	t-value	p-value
NETRIN1 gMD	2.53E-06	1.42E-06	1.78E+00	7.47E-02
NETRIN1 Association fibres	1.43E-06	1.08E-06	1.33E+00	1.84E-01
NETRIN1 Thalamic radiations	1.71E-06	7.87E-07	2.17E+00	3.01E-02
NETRIN1 Projection fibres	9.36E-07	8.00E-07	1.17E+00	2.42E-01
Genomic gMD	1.50E-06	1.43E-06	1.04E+00	2.96E-01
Genomic Association fibres	1.66E-06	1.09E-06	1.53E+00	1.27E-01
Genomic Thalamic radiations	3.99E-08	7.93E-07	5.02E-02	9.60E-01
Genomic Projection fibres	9.47E-07	8.06E-07	1.17E+00	2.40E-01

Results depicted in tables S6 – S21 indicate secondary analyses which complement our primary analyses. These consist firstly of the effect unpruned NETRIN1- and genomic-PRS on FA and MD values, conducted on both the full dataset (N = 6,420) and the dataset with excluded outliers (N = 6,401 and 6,390 for FA and MD, respectively). Secondly, we also investigated the effect of pruned NETRIN1- and genomic-PRS on FA and MD values, again conducted on both the full dataset and dataset with excluded outliers. The analyses consist of PRS at all five p-value thresholds (0.01, 0.05, 0.1, 0.5 and 1). A similar pattern is observed for significance in white matter tracts associated with both PRS lists across PRS thresholds within the dataset with outliers removed. Some tracts remain significant within the full sample dataset as compared to the sample with outliers removed at PRS threshold 0.5, however there is a trend towards more significant results when outliers are removed. Please refer to tables S8-S9, S12-S13, S16-S17 and S20-S21 for an account of results at PRS threshold 0.5 within the full dataset, which are directly comparable to the primary results depicted in the manuscript (PRS threshold 0.5 with outliers removed).

White matter tracts significantly associated with both NETRIN1-PRS and genomic-PRS

Fractional anisotropy

Tract categories

Significantly lower FA values in association fibres were found for both NETRIN1-PRS ($\beta = -0.032$, $p_{\text{corrected}} = 0.023$) and genomic-PRS ($\beta = -0.033$, $p_{\text{corrected}} = 0.011$).

Mean diffusivity

Global measures

Significantly higher gMD was associated with both NETRIN1-PRS ($\beta = 0.027$, $p_{\text{corrected}} = 0.031$) and genomic-PRS ($\beta = 0.033$, $p_{\text{corrected}} = 0.006$).

Individual white matter tracts

Significantly higher MD in the inferior fronto-occipital fasciculus was found for both NETRIN1-PRS ($\beta = 0.027$, $p_{\text{corrected}} = 0.046$) and genomic-PRS ($\beta = 0.031$, $p_{\text{corrected}} = 0.018$).

Data analysis code – example

```
##### NETRIN1 & Genomic-PRS analysis #####

# PREP DATA - READ IN FILES & APPLY PCA FOR REMOVING OUTLIERS

library(dplyr)
Library(nlme)

# Read in PRS lists and imaging data

# OUTLIER EXCLUSION - FA (apply PCA on all regions in original dataset)

IM.measure = 'FA.wm' # for FA white matter tracts
dat_sub=targetdata[,c(1,grep(IM.measure,colnames(targetdata)),865:ncol(targetdata))]
dat_sub=dat_sub[complete.cases(dat_sub[,grep(IM.measure,colnames(dat_sub))]),]

targetdata=dat_sub
pca_data = targetdata[,c(grep(IM.measure,colnames(targetdata)))]
pca_fit <- princomp((-1*pca_data), scores = TRUE)
pca_score <- pca_fit$scores[,1]
dat_outlier_clear=targetdata[(scale(pca_score)> -3)&(scale(pca_score)<3),]

#####

# Read in dataset containing unrelated British individual to exclude related individuals

#Merge NETRIN1 PGRS with target imaging data

#UKB_merge1 = merge(UKB_subset,NETRIN1_pgrs,by="f.eid",all.x=TRUE)

# Read in: MRI position covariates, descriptive statistics (age, sex, etc.), principal
components, genotype array

# Merge imaging with all covariates that were read in above

# Example: Merge baseline with UKB_merge1 (containing PRS and imaging data)

baseline = data.frame(baseline[,1:2])
colnames(baseline)[2] <- "sex"
UKB_merge4 = merge(UKB_merge1,baseline,by="f.eid",all.x=TRUE)

# And do the same for all other covariates
```


SCALE DEPENDENT AND INDEPENDENT VARIABLES BEFORE PUTTING THEM IN LONG FORMAT

```

UKB_final[,c(2:28,31:40)] <- scale(UKB_final[,c(2:28,31:40)]) #2:28 are the white matter
tracts, while 31:40 are the NETRIN1 PGRS
##### Prep long format data ##### output: data_long

# settings; change colnames of non-imaging data and imaging data according to the dataset
you are using - with or without outliers

targetdata = UKB_final
cols_nonimg = colnames(targetdata)[29:ncol(targetdata)] # colnames of non-imaging data
dat_colnames = colnames(targetdata)[2:28] # colnames of imaging data
measures = c('FA.wm')

#=====
=====#
source('/path/to/script/long_format.R')
dat_long <- long_format(targetdata,cols_nonimg,cols_img,measures)

# set the data in regression format
# the sequence of data from left to right:
# f.eid || factors || dependent variables || covariates
# Order the column numbers below according to the variables above: f.eid first, then factors
(PGRS lists),
# then dependent variables (DTI variables in this case), and then covariates (age, sex, 15 PCs,
genotype array, hemisphere)
# (factors=the last input of an equation)

targetdata_long = dat_long[,c(1,16:25,2:13,15,26,28:30,27,31:34,35:49,50)] # long-format
data
#This includes: f.eid, 10 PGRS lists, 12 bilateral DTI measures, MRI age calculated,
#sex, pos_covar, array, PCs & hemi
targetdata_long = targetdata_long[complete.cases(targetdata_long),] #complete cases for all
variables

targetdata_short = UKB_final[,c(1,31:40,2:28,30,41,43:45,42,46:49,50:64)] # short-format
data for outliers excluded
targetdata_short = targetdata_short[complete.cases(targetdata_short),] #complete cases for all
variables

# REGRESSION ANALYSIS
# FA - 0.5; use targetdata_long and targetdata_short (depending on white matter tract) for
analysis

WM_list <- colnames(targetdata_long)[2:13] # select all WM tracts to run regression
no_WM_list <- length(WM_list) # assign length of columns

# create a named list to hold the fitted models
fitlist <- as.list(1:no_WM_list)

```

```

names(fitlist) <- WM_list

for(i in WM_list){
  # create temporary data matrix and model formula
  tmp <- targetdata_long[, c(i,"sex","MRI_age.calculated","pc1","pc2","pc3","pc4",
    "pc5","pc6","pc7","pc8","pc9","pc10","pc11","pc12","pc13","pc14","pc15",
    "genotyping.array",
    "pos.x", "pos.y",
    "pos.z","NETRIN1_WG_pT_0.5","NETRIN1_pathway_pT_0.5","f.eid")]
  fml <- as.formula( paste(i, "~",
    paste(c("sex","I(MRI_age.calculated^2)","MRI_age.calculated","pc1","pc2",
    "pc3","pc4","pc5","pc6","pc7","pc8","pc9",
    "pc10","pc11","pc12","pc13","pc14","pc15","genotyping.array","pos.x",
    "pos.y",
    "pos.z","hemi","NETRIN1_WG_pT_0.5","NETRIN1_pathway_pT_0.5"), collapse="+") ) )
  # assign fit to list by name
  fitlist[[i]] <- lme(fml, random=~1|f.eid,na.action=na.exclude,control=lmeControl(opt =
  "optim"), data=tmp)
}

FA_0.5 <- lapply(fitlist, summary)

# FDR correction – conducted separately for NETRIN1 and Genomic-PRS p-values

# INDIVIDUAL WHITE MATTER TRACTS

FA_Pvalues_categories_ind_tracts$p.corrected_fdr =
  p.adjust(FA_Pvalues_categories_ind_tracts$V2,
    method = "fdr")

write.table(FA_Pvalues_categories_ind_tracts, "FA_ind_tract_FDR_Pvalue",sep="\t")

# TRACT CATEGORIES

FA_Pvalues_categories_gFA$p.corrected_fdr =
  p.adjust(FA_Pvalues_categories_gFA$V2,
    method = "fdr")

write.table(FA_Pvalues_categories_gFA, "FA_categories_FDR_Pvalue",sep="\t")

```

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