Disruptions in White Matter Maturation and Mediation of Cognitive Development in Youths on the Psychosis Spectrum

Supplementary Information

Exclusion Criteria

PNC-defined exclusion criteria included major medical problems that could affect brain function, including major severe medical problems (malignancy, immunological disorders, renal/hepatic compromise), neurological conditions (stroke, meningitis, epilepsy, brain tumors, traumatic brain injury), or endocrine (including thyroid or adrenal abnormalities). Participants were also excluded if they had impaired vision or hearing, implanted ferrous metal and other contraindications to MRI. In addition to these criteria, we excluded individuals who endorsed a frequency and duration of symptoms consistent with other DSM-IV psychiatric disorders, including mood, anxiety, behavioral, substance abuse and eating disorders. Consistent with previous PNC publications (1-3), psychopathology for one of these disorders was considered to be significant if symptoms endorsed were consisted with frequency and duration of a DSM-IV psychiatric disorder, while correspondingly accompanied by significant distress or impairment (a rating of $\geq$5 on a scale of 0-10).

Subclinical Grouping

Psychosis was assessed using the PrimeScreen-Revised (PS-R), in which subjects rate 12 items related to positive symptoms on a 7-point scale from 0 (“definitely disagree”) to 6 (“definitely agree”) (4, 5), the Scale of Prodromal Syndromes (SOPS, (6)), and a computerized version of selected items from the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS,(7, 8)). Consistent with previous categorization in this sample (2, 4), individuals were classified as psychosis spectrum (PS) if any one of several criteria were met: 1) a total score two age-standard deviations (SDs) above the age-mean for PS-R, 2) a rating of at least six for one PS-R item, 3)

at least three PS-R items rated as equal or greater to a five in severity, 4) endorsed any hallucination on the K-SADS, which was not attributable to drug use and caused significant problems or distress, or 5) a score more than two age-SDs above the age-mean for the total SOPS score. Individuals were classified as limited psychosis spectrum (LPS) if they did not meet criteria for PS, and had over 1 age-SD from the age-mean for the total score on either the PS-R or SOPS. Participants not meeting exclusion criteria or criteria for either PS or LPS were classified as typically developing (TD).

Imaging Protocol

All imaging data were acquired on a single 3T Siemens TIM Trio whole-body scanner using the VB17 revision of the Siemen's software as part of the PNC protocol at the University of Pennsylvania. A 32-channel head coil was used for receiving signal. All scans were acquired with a non-oblique axial orientation. To reduce the length of the scan, the DTI sequence was broken into two imaging runs, thus the 64-direction scan was divided into two scans, each with 32 diffusion-weighted directions chosen to be maximally independent so as to separately sample the surface of a sphere. The first set (TR/TE/TI(ms) = 8100/82, FOV RL/AP = 240/240, Matrix RL/AP/slices = 128/128/70, slice thick/gap (mm) = 2/0, Flip angle = 90/180/180, repetitions = 35, GRA PPA factor = 3, BW/pixel = 2170, PE direction = AP, Acquisition time = 5:24) contained three b=0 acquisitions, and the second set (TR/TE/TI(ms) = 8100/82, FOV RL/AP = 240/240, Matrix RL/AP/slices = 128/128/70, slice thick/gap (mm) = 2/0, Flip angle = 90/180/180, repetitions = 36, GRA PPA factor = 3, BW/pixel = 2170, PE direction = AP, Acquisition time = 5:32) contained four b=0 acquisitions.

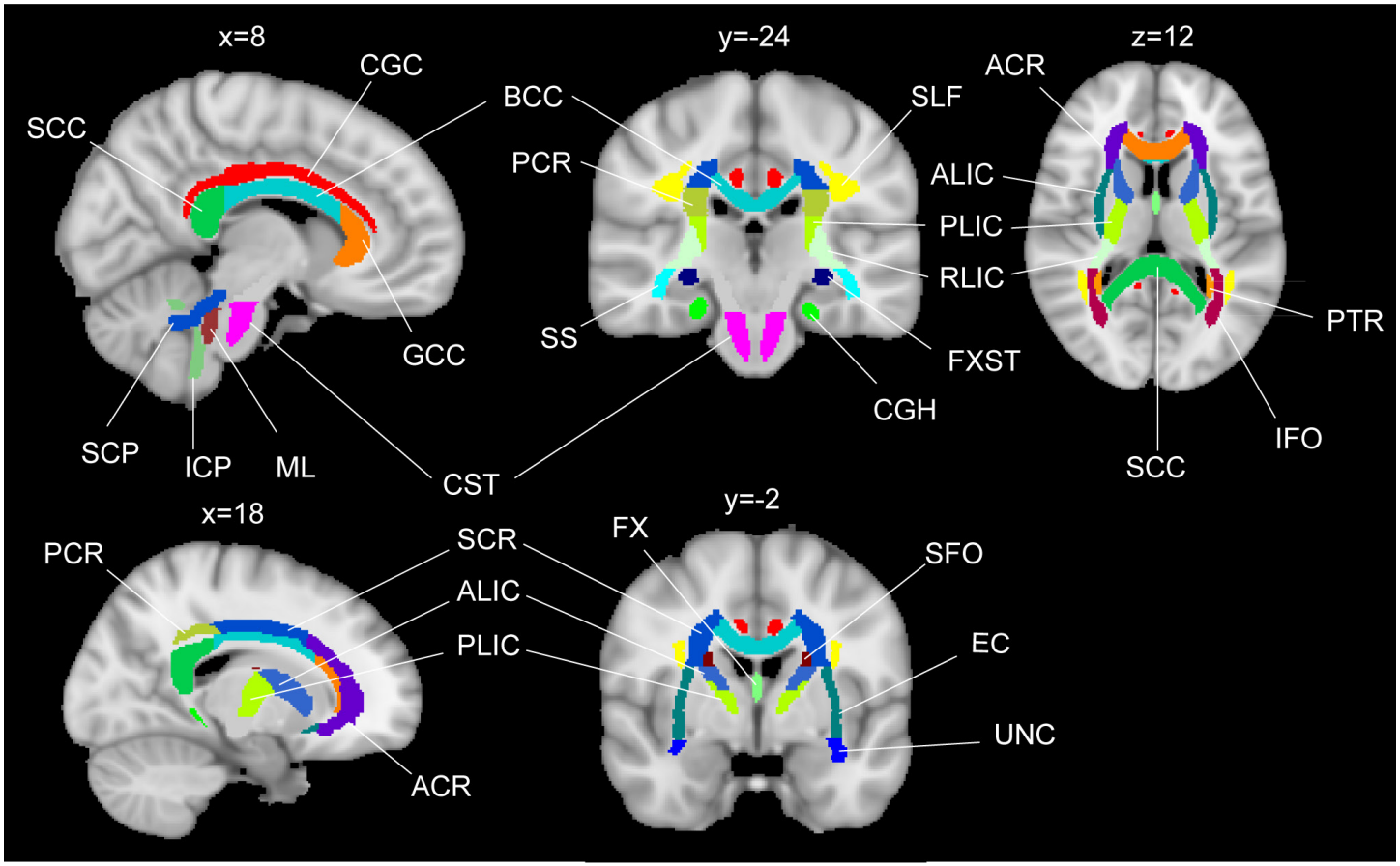

Figure S1. Regions of interest. Abbreviations: FA=fractional anisotropy, SD=standard deviation, ACR=anterior corona radiata, ALIC=anterior limb of internal capsule, BCC=body of corpus callosum, CC=corpus callosum, CGC=cingulum, CGH=cingulum (hippocampal portion), CR=corona radiata, CST=corticospinal tract, EC=external capsule, FA=fractional anisotropy, FX=fornix, FXST=fornix stria terminalis, GCC=genu of corpus callosum, IC=internal capsule, IFO=inferior fronto occipital fasciculus, PCR=posterior corona radiata, PLIC=posterior limb of internal capsule, PTR=posterior thalamic radiation, RLIC=retrolenticular part of IC, ROI=region of interest, SCC=splenium of corpus callosum, SCR=superior corona radiata, SFO=superior fronto-occipital fasciculus, SLF=superior longitudinal fasciculus, SS=sagittal stratum, UNC=uncinate.

Table S1. **Main effect of group for each ENIGMA tract from regression analyses.** Regression analyses for each tract included sex, age, group (TD and PS) and age x group interaction terms.

	n[a]		Mean ± SD			
ROI	TD	PS	TD	PS	Statistic	p-value[b]
Average FA	492	168	0.44±0.015	0.436±0.015	F(1,655)=1.74	0.1884
ACR	493	170	0.44±0.024	0.438±0.024	F(1,658)=4.85	0.028
CC	490	168	0.705±0.023	0.701±0.023	F(1,653)=0.766	0.09
BCC	492	171	0.664±0.032	0.657±0.031	F(1,658)=1.43	0.2328
GCC	494	170	0.715±0.027	0.713±0.029	F(1,659)=1.59	0.2076
ALIC	492	169	0.558±0.023	0.556±0.025	$F(1,656)=3.5x10^{-5}$	0.992
CR	492	168	0.471±0.02	0.469±0.02	F(1,655)=5.27	0.022
FXST	494	170	0.528±0.029	0.523±0.027	F(1,659)=0.12	0.732
FX	491	167	0.483±0.043	0.476±0.044	F(1,653)=0.45	0.504
PTR	498	168	0.624±0.029	0.618±0.030	F(1,661)=6.21	0.0132
SS	491	170	0.549±0.024	0.542±0.028	F(1,656)=0.19	0.668
SFO	493	171	0.511±0.028	0.508±0.032	F(1,659)=0.95	0.3308
CGC	495	171	0.587±0.039	0.586±0.04	F(1,661)=0.12	0.7244
PCR	493	168	0.491±0.026	0.484±0.025	F(1,656)=2.94	0.0868
SCC	488	167	0.754±0.019	0.751±0.022	F(1,650)=6.69	0.00992
SLF*	496	169	0.510±0.026	0.505±0.025	F(1,660)=10.12	0.00152
EC	493	167	0.449±0.020	0.446±0.020	F(1,655)=0.01	0.936
IC	494	168	0.605±0.018	0.600±0.018	F(1,657)=0.10	0.756
UNC	496	171	0.553±0.045	0.548±0.047	F(1,662)=0.62	0.432
SCR	491	168	0.49±0.023	0.489±0.022	F(1,654)=3.59	0.0588
RLIC	495	167	0.584±0.024	0.578±0.024	F(1,657)=6.77	0.0096
IFO	492	170	0.501±0.034	0.500±0.038	F(1,657)=1.13	0.2876
CGH	498	168	0.455±0.038	0.452±0.041	F(1,661)=1.04	0.308
CST	484	165	0.519±0.036	0.511±0.039	F(1,644)=0.23	0.632
PLIC	493	168	0.663±0.021	0.659±0.02	F(1,656)=0.52	0.468

[a]Sample size used for regression analyses after excluding outliers. [b]Corrected significance threshold of p<0.002 (0.05/25). *indicates significant effect of group at corrected threshold (p<0.002).

Abbreviations: FA=fractional anisotropy, SD=standard deviation, ACR=anterior corona radiata, ALIC=anterior limb of internal capsule, BCC=body of corpus callosum, CC=corpus callosum, CGC=cingulum, CGH=cingulum (hippocampal portion), CR=corona radiata, CST=corticospinal tract, EC=external capsule, FA=fractional anisotropy, FX=fornix, FXST=fornix stria terminalis, GCC=genu of corpus callosum, IC=internal capsule, IFO=inferior fronto occipital fasciculus, PCR=posterior corona radiata, PLIC=posterior limb of internal capsule, PTR=posterior thalamic radiation, RLIC=retrolenticular part of IC, ROI=region of interest, SCC=splenium of corpus callosum, SCR=superior corona radiata, SFO=superior fronto-occipital fasciculus, SLF=superior longitudinal fasciculus, SS=sagittal stratum, UNC=uncinate.

Table S2. Additional age x group interactions on regional FA. The splenium of the corpus callosum (SCC) and posterior thalamic radiation (PTR) reached trend-level significance for an age x group (TD and PS) interaction on FA after Bonferroni correction ($p < 0.004$). Four additional tracts reached uncorrected significance ($p<0.05$; anterior corona radiata [ACR], corona radiata [CR], posterior corona radiata [PCR], and superior corona radiata [SCR]).

ROI	Statistic	p[a]
SCC*	F(1,650)=8.88	0.0030
PTR*	F(1,661)=9.01	0.0028
CR	F(1,655)=6.80	0.0093
ACR	F(1,658)=5.66	0.0176
PCR	F(1,656)=5.50	0.0193
SCR	F(1,654)=3.93	0.0477

[a] Uncorrected p-value
*Significant at trend-level corrected threshold ($p<0.004=0.10/25$).

Table S3. Contribution of individual variables in SLF regression model.

	Coefficient	Std. Error	t	P>|t|	95% Confidence Interval	
Sex	0.0082	0.0019	4.24	2.5×10^{-5}	0.0044	0.012
Age	0.0031	0.0003	9.3	2.08×10^{-19}	0.00024	0.0038
Group	0.0382	0.012	3.18	0.0015	0.0146	0.0618
Age x Group	-0.0027	0.00075	-3.63	3.01×10^{-4}	-0.0042	-0.0012

Table S4. Contribution of individual variables in RLIC regression model.

	Coefficient	Std. Error	t	P>|t|	95% Confidence Interval	
Sex	7.89x10-4	0.0019	-0.42	0.676	-0.0045	0.0028
Age	0.0011	3.22x10-4	3.42	0.001	0.00047	0.0017
Group	0.0304	0.0117	2.6	0.009	0.0075	0.0533
Age x Group	-0.0023	0.00073	-3.23	0.001	-0.0038	-0.00091

Table S5. **Univariate tests comparing efficiency in cognitive domains were conducted using age and sex as covariates and group as a fixed factor.** Significance values were Bonferroni corrected for the four cognitive domains.

	n		Group (Mean Efficiency[a] ± SD)			
Cognitive Domain	TD	PS	TD	PS	Statistic	Significance[b]
Executive Control	493	166	0.428±0.940	0.098±1.04	F(1,655)=17.28	$3.70x10^{-5}$
Complex Cognition	494	167	0.387±0.829	-0.036±0.969	F(1,657)=31.86	$3.94x10^{-9}$
Episodic Memory	498	170	0.404±1.08	0.065±1.43	F(1,664)=11.73	$1.60x10^{-4}$
Social Cognition	168	498	0.204±0.932	0.009±0.865	F(1,662)=8.36	0.004

[a]Mean Efficiency reflects the average Z-Score (sum of Z-score for accuracy and -1 multiplied by Z-score for speed) per group, such that higher scores indicate better performance. [b]Corrected significance threshold p<0.0125 (=0.05/4).
Abbreviations: TD=typically developing, PS=psychosis spectrum.

Table S6. Mediation analysis results for TD youth.

	Path Coefficients (SE)					Percent of Total Effect Mediated	Bootstrap 99% CI
	age à SLF	SLF à Cognition	Direct Effect	Total Effect	Mediated Effect		
Dependent Variable	*a*	*b*	*c'*	*c=ab+c'*	*ab*		
Complex Cognition[a, †]	0.0030** (0.0003)	6.377** (1.415)	0.0492** (0.0113)	0.0683** (0.0107)	0.0189[†] (0.0047)	27.6	0.0066, 0.0311
Executive Control[b]	0.0030** (0.0034)	1.652 (1.536)	0.115** (0.0123)	0.120** (0.012*)*	0.0050 (0.0047)	4.14	-0.0074, 0.0173
Social Cognition[c]	0.0031** (0.0003)	0.8198 (1.518)	0.119** (0.0123)	0.1216** (0.0113)	0.0025 (0.0047)	2.06	-0.0097, 0.0147
Episodic Memory[d]	0.0031** (0.0003)	3.763* (1.85)	0.0860** (0.0149)	0.0975** (0.014)	0.0115 (0.0058)	11.8	-0.0055, 0.0285

*p<0.05, **p<0.001, [†] mediation effect significant at 99% CI.
[a]n=491, [b]n=490, [c]n=495, [d]n=495.
Abbreviations: TD=typically developing, SLF=superior longitudinal fasciculus, CI=confidence interval.

Table S7. Non-FA mediation analysis results for TD youth.

	Path Coefficients (SE)					Percent of Total Effect	
	age à SLF	SLF à Cognition	Direct Effect	Total Effect	Mediated Effect		Bootstrap
Dependent Variable	*a*	*b*	*c'*	*c=ab+c'*	*ab*	Mediated	99% CI
Radial Diffusivity†	-4.5x10^{-6}** (3.6x10^{-7})	-4919.18** (1322.15)	0.0487** (0.0113)	0.0709** (0.0107)	0.0222** (0.0062)	31.3	0.0060, 0.0384
Axial Diffusivity	-2.4x10^{-6}** (4.3x10^{-7})	2649.8* (1119.4)	0.0776** (0.0110)	0.0713** (0.0107)	-0.0063* (0.0029)	8.85	-0.0140, 0.0015

Abbreviations: TD=typically developing, SLF=superior longitudinal fasciculus, CI=confidence interval.

Table S8. Mediation analysis of complex cognition speed and accuracy for TD youth.

	Path Coefficients (SE)					Percent of Total Effect	
	age à SLF	SLF à Cognition	Direct Effect	Total Effect	Mediated Effect		Bootstrap
Dependent Variable	*a*	*b*	*c'*	*c=ab+c'*	*ab*	Mediated	99% CI
Accuracy†	0.0030** (0.0003)	5.193** (1.279)	0.0632** (0.0102)	0.0785** (0.0096)	0.0154** (0.0062)	19.6	0.0041, 0.0266
Speed	0.0030** (0.0003)	1.252 (1.019)	-0.0138 (0.0081)	-0.0101 (0.0076)	0.0037 (0.0030)	NA	NA

Abbreviations: TD=typically developing, SLF=superior longitudinal fasciculus, CI=confidence interval.

Supplemental References

1. Satterthwaite TD, Wolf DH, Calkins ME, Vandekar SN, Erus G, Ruparel K, et al. (2016): Structural Brain Abnormalities in Youth With Psychosis Spectrum Symptoms. *JAMA Psychiatry*. 73:515-524.
2. Calkins ME, Moore TM, Merikangas KR, Burstein M, Satterthwaite TD, Bilker WB, et al. (2014): The psychosis spectrum in a young U.S. community sample: findings from the Philadelphia Neurodevelopmental Cohort. *World Psychiatry*. 13:296-305.
3. Calkins ME, Moore TM, Satterthwaite TD, Wolf DH, Turetsky BI, Roalf DR, et al. (2017): Persistence of psychosis spectrum symptoms in the Philadelphia Neurodevelopmental Cohort: a prospective two-year follow-up. *World Psychiatry*. 16:62-76.
4. Miller TJ, Cicchetti D, Markovich PJ, McGlashan TH, Woods SW (2004): The SIPS screen: a brief self-report screen to detect the schizophrenia prodrome. *Schizophrenia Res*. 70:78.
5. Kobayashi H, Nemoto T, Koshikawa H, Osono Y, Yamazawa R, Murakami M, et al. (2008): A self-reported instrument for prodromal symptoms of psychosis: testing the clinical validity of the PRIME Screen-Revised (PS-R) in a Japanese population. *Schizophr Res*. 106:356-362.
6. McGlashan TH, Miller TJ, Woods SW (2003): *Structured Interview for Prodromal Syndromes, Version 4.0.* Version 4.0 ed. New Haven, CT: PRIME Clinic Yale School of Medicine.
7. Merikangas KR, Dierker LC, Szatmari P (1998): Psychopathology among offspring of parents with substance abuse and/or anxiety disorders: a high-risk study. *J Child Psychol Psychiatry*. 39:711-720.
8. Merikangas K, Avenevoli S, Costello J, Koretz D, Kessler RC (2009): National comorbidity survey replication adolescent supplement (NCS-A): I. Background and measures. *J Am Acad Child Adolesc Psychiatry*. 48:367-369.