Data supplement for Huang et al., Thalamic Nuclei Volumes in Psychotic Disorders and in Youths With Psychosis Spectrum Symptoms. Am J Psychiatry (doi: 10.1176/appi.ajp.2020.19101099)

SUPPLEMENTAL METHODS

Study Procedures: Psychosis Cohort

Of the initial 593 participants, six participants did not complete scanning, 17 subjects were found ineligible during the course of the study, and 113 subjects were excluded for scan or segmentation quality. Fifteen subjects met multiple exclusion criteria. Individuals with a psychotic disorder were recruited from the psychiatric inpatient and outpatient clinics of the Vanderbilt University Medical Center Psychotic Disorders Program and healthy individuals were recruited from Nashville and the surrounding community via advertisements and word of mouth.

Diagnoses were confirmed, or ruled out in the case of healthy participants, using the Structured Clinical Interview for DSM-IV (1). Clinical symptoms were further assessed with the Positive and Negative Syndrome Scale (2) (PANSS). Premorbid IQ was estimated with the Wechsler Test of Adult Reading (3) (WTAR) and current neuropsychological functioning was assessed with the Screen for Cognitive Impairment in Psychiatry (4) (SCIP). Exclusion criteria were similar across all three studies. Participants were excluded for: significant medical or neurological illness, head injury, pregnancy, age <16 and >65, premorbid IQ less than 65, substance abuse or dependence (at least one month in patients, lifetime in healthy individuals), and any MRI contra-indicators. Healthy individuals were excluded if they had current or past psychiatric illness or a first degree relative with a psychotic illness. Healthy individuals were recruited to match the psychosis group for age, gender, race and parental education.

Study Procedures: Philadelphia Neurodevelopmental Cohort

The Philadelphia Neurodevelopmental Cohort (PNC) is a community cohort, which differs from high-risk, help seeking samples of youth in that there will be a wider range of symptom severity and overall less severe symptoms. Clinical assessments included structured interviews and rating scales as described previously (5). In brief, study participants were assessed with the

GOASSES, a computerized structured clinical interview that includes collecting demographic data, a timeline of life events, medical history, and an abbreviated version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) to assess a range of psychopathology (6). In addition, the PRIME Screen-Revised (PS-R), K-SADS psychosis screen, and selected items from the Scale for Prodromal Syndromes (SOPS) assessing negative/disorganized symptoms were administered to assess a broad range of psychosis spectrum symptoms. The PS-R consists of 12 self-rated items assessing sub-threshold positive symptoms experienced in the past year. Each item is rated on a 7-point scale where 0=Definitely Disagree and 6=Definitely Agree and a total score was calculated by summing the 12 items. The K-SADS psychosis screen assesses for positive psychosis symptoms—hallucinations and delusions specifically. Negative/disorganized items administered from the SOPS included: N2 Avolition, N3 Expression of Emotion, N4 Experience of Emotions and Self, N6 Occupational Functioning, D3 Trouble with Focus and Attention, and P5 Disorganized Communication. A SOPS total score was calculated by summing the 6 items.

Youth were classified as psychosis spectrum using the same criteria as previously described (5). Briefly, individuals were classified as psychosis spectrum if they; 1) had an age-deviant PRIME total score >=2 SD above age-matched peers or had one or more PRIME items rated 6, or 3 or more items rated 5; 2) endorsed definite or possible hallucinations or delusions on the K-SADS psychosis screen; or 3) had an age-deviant SOPS negative/disorganized score >=2 SD above age-matched peers.

Youth with other psychopathologies were defined as those that had sub-threshold psychopathology symptoms—endorsed symptoms, frequency, and duration approximate with DSM-IV disorders or episode criteria, with significant distress (≥5) on the K-SADS—but did not meet psychosis criteria.

Typically developing youth were defined as those that did not meet criteria for either psychosis or other psychopathologies.

Of the 1601 participants with imaging data, 73 were excluded for serious medical conditions, 63 for insufficient clinical data to reach a diagnosis and 72 for poor scan and/or segmentation quality. A small number of individuals from each group were taking psychotropic medications (typically developing: n=16; psychosis spectrum: n=71; other psychopathologies: n=49).

PNC Sensitivity Analysis

As we observed group differences in age, sex and race, we ran a sensitivity analysis by creating sub-samples of the psychosis spectrum and typically developing youth matched for age, sex and race. Matching was conducted using the MatchIt package (7) (Version 3.0.2) in R (Version 3.6.1; R Core Team, 2019), using the 'exact' matching method, which matches each member of the typically developing youth with any psychosis spectrum youth that have the same values for age, sex and race. Race was considered as a binary variable, separated into Caucasian and non-Caucasian youth. This resulted in a final sample of 150 psychosis spectrum and 133 typically developing youth. See Table S2 for demographics.

Hemisphere Effects Analyses

For each of the 5 nuclei, we tested the effect of hemisphere, and hemisphere by group interactions with ANCOVAs, including hemisphere as a repeated measure and group as independent measures. For all analyses, age, sex, ICV, and project for the psychosis cohort were included as covariates of no interest.

Age and Sex Effect Analyses

Separate analyses were conducted to test for the effect of age and sex in both the psychosis cohort and PNC.

Age effects were examined in separate linear regression models with thalamic nucleus volume as the outcome variable; age and age by group interactions as the predictors. Sex, ICV, and project for the psychosis cohort were included as covariates.

Sex effects were examined in separate univariate analyses with thalamic nucleus volume as the dependent variable; sex and group as independent variables. Age, ICV and project for the psychosis cohort were included as covariates.

Scan parameters

A T1-weighted anatomical image was collected on all subjects in both cohorts during a single scanning session.

Psychosis cohort: High resolution T1-weighted structural scans were collected with a 3D T1 fast field echo sequence with 1 mm^3 isotropic voxels across 2 sequences. Scan Sequence 1: 170 slices, TR/TE = 8.9/4.6, FOV = 256 x 256 x 170 mm, matrix = 256 x 256 x 170, flip angle = 8°; and Scan Sequence 2: 170 slices, TR/TE = 8.0/3.7, FOV=256 x 256 x 170 mm, matrix = 256 x 256 x 170, flip angle = 5°.

PNC: High resolution T1-weighted structural scans were acquired with the MPRAGE sequence on a Siemens Tim Trio 3T scanner with a 32-channel head coil with the sequence: 0.93 x 0.93 x 1 mm voxels, 160 slices, TR/TE = 1810/3.5, FOV = 180 x 240 x 160, matrix = 192 x 256 x 160; flip angle = 9°.

FreeSurfer Segmentations

Each T1 image was processed using the FreeSurfer 6 image analysis suite with standard parameters (8, 9) (http://surfer.nmr.mgh.harvard.edu/) and the thalamic nuclei segmentation module (10). This module performs automated segmentation of 25 thalamic subdivisions based on a high-resolution probabilistic atlas generated from ex vivo MRI and histology data. Prior to analysis, T1 images were visually inspected for quality, blind to group membership, and any scans with significant motion or artefacts were excluded from analyses. After running the FreeSurfer thalamus segmentation module, thalamus segmentations were visually inspected for quality (see Figures S1–S4 for examples), specifically to ensure that the whole thalamus was captured and that significant voxels outside the thalamus were not included. Individual thalamic nuclei segmentations were not considered during visual inspection, as we did not wish to bias our final analysis.

Five thalamic nuclei were created by combining volumes from the sub-divisions that make up these nuclei. These five nuclei were selected a priori based on the following criteria. First, we restricted our selection to the largest thalamic nuclei/nuclei groups for inclusion, as the 1mm^3

resolution available in our T1 structural images are not ideal for resolving smaller nuclei. Second, following advice from the developers, we excluded the lateral and medial geniculate nuclei due to lack of contrast with surrounding white matter. The thalamic nuclei we created were as follows: 1) the mediodorsal nucleus composed of the bilateral MDm and MDl subdivisions; 2) the pulvinar nucleus composed of the bilateral PuL, PuI, PuA and PuM subdivisions; 3) the ventrolateral nucleus composed of the bilateral VLa and VLp subdivisions; 4) the ventral anterior nucleus composed of the bilateral VA and VAmc subdivisions and 5) the ventral posterolateral nucleus composed of the bilateral VPL subdivisions. The intralaminar nuclei and anterior ventral nucleus were excluded as we believe they are too small to be appropriately segmented in a T1 image with 1 mm^3 resolution. Visual inspection in this dataset confirmed that the medial and lateral geniculate nuclei were not well segmented in most subjects.

Voxel-based Morphometry

Voxel-based Morphometry (VBM) was used to investigate voxel-wise volume reduction in the thalamus using the Computational Anatomy Toolbox 12 (CAT12: Version 12.5) in Statistical Parametric Mapping 12 (SPM12: Version 7487). T1 images were visually inspected for quality and any scans with significant motion or artifacts were excluded. T1-weighted structural images were corrected for bias-field inhomogeneities, registered using linear (12-parameter affine) and non-linear transformations then spatially normalized using the DARTEL algorithm (11), and segmented into gray matter, white matter and cerebrospinal fluid (12). CAT12 provides a quantitative measure of image quality based on a retrospective quality assurance framework that evaluates image parameters such as noise, inhomogeneities and image resolution. This measure provided is placed on a rating scale and assigned a letter grade, with any scan rated B- or above considered good quality and scans rated C- to C+ considered satisfactory. In our data, all CAT12 output rated C+ or below were further visually inspected, blind to group membership, for grey matter segmentation quality (see Figure S5 for examples). Any scans with grey matter segmentation that did not capture the grey matter, or included non grey matter voxels, were excluded from further analysis. The modulated, normalized gray matter segmentations were checked with the CAT12 automated quality check protocol, which checks image inhomogeneity. All flagged images were visually inspected, and any scans with significant inhomogeneity were excluded from further analysis. Modulated grey matter segmentations were then smoothed with a 4 mm FWHM gaussian and entered into one-way

ANOVAs with age, sex, total ICV (calculated in CAT12), and project for the psychosis cohort included as covariates. Given our a priori focus on the thalamus, group analyses were masked to include only voxels in the whole thalamus. Briefly, whole thalamus masks were created by converting each subjects' FreeSurfer standard whole thalamus segmentation into MNI space, then averaging across all subjects to create the resulting mask. This was done separately for the psychosis and PNC cohorts. We chose this approach rather than use a mask from publicly-available atlases (e.g. Harvard-Oxford atlas) as it best approximates our data, including age differences between the psychosis cohort and PNC (e.g. adults vs. youth) and differences between datasets in scanning parameters.

SUPPLEMENTAL RESULTS

Psychosis Cohort: Supplementary Analyses

Group Effect Separating Psychosis by Schizophrenia Spectrum and Psychotic Bipolar Disorder: The analysis of healthy individuals against schizophrenia and psychotic bipolar disorder groups showed a main effect of group ($F(2,464)=7.945$, $p<.001$), and a nuclei by group interaction ($F(8,1856)=5.182$, $p<.001$). Demographics are presented in Table S1. Post hoc analyses of group effects in individual nuclei showed a significant group effect in the MD ($F(2,464)=8.066$, $p<.001$). As seen in Figure S6, healthy individuals showed significantly larger volumes compared to those with a schizophrenia spectrum diagnosis ($p<.001$) and those with psychotic bipolar disorder ($p=.02$). No significant difference between individuals with schizophrenia spectrum and psychotic bipolar disorder was observed ($p=.43$). A significant group effect was also observed in the pulvinar ($F(2,464)=9.928$, $p<.001$), with healthy individuals showing significantly larger volumes than those with a schizophrenia spectrum diagnosis ($p<.001$), but not individuals with psychotic bipolar disorder ($p=.16$). There was a significant difference between individuals with a schizophrenia spectrum diagnosis and psychotic bipolar disorder ($p=.03$). There was no significant group effect in the ventral lateral nucleus ($F(2,464)=3.741$, $p=.02$; critical alpha = .01) when schizophrenia spectrum and psychotic bipolar disorder were considered separately. Examination of the LSD post hoc analysis showed a trend towards significance in both the schizophrenia spectrum ($p=.01$) and psychotic bipolar disorder ($p=.04$) groups, suggesting that when combined into a psychosis population, the increase in power may explain the significant group effect observed in the comparison between healthy individuals and individuals with psychosis. Neither the ventral anterior nucleus ($F(2,464)=1.863$, $p=.16$) nor the ventral posterolateral nuclei ($F(2,464)=2.881$, $p=.06$) showed a group effect. Mean volumes for both the main analysis and this one separating psychosis into schizophrenia spectrum and psychotic bipolar disorder are presented in Tables S3 and S4.

Whole Thalamus effects: An examination of whole thalamus volumes showed a main effect of group, with the psychosis group showing smaller thalamus volumes than the healthy group ($F(1,465)=16.063$, $p<.001$).

Hemisphere effects: There was no significant main effect of hemisphere in any nucleus (all p's>.05), or group by hemisphere interaction (all p's>.1) in any nucleus. See Table S11 for mean volumes of each hemisphere and full statistical results.

Age effects: As seen in Figure S8, there was a significant main effect of age in all thalamic nuclei, with older participants showing smaller volumes, but no age by group interactions in any thalamic nuclei. See Table S12 for full statistical results.

Sex effects: There was a significant main effect of sex in all thalamic nuclei, with females showing smaller volumes in all nuclei, after adjusting for age, ICV and project. There was no group by sex interaction in any of the nuclei. See Table S13 for full statistical results.

Clinical correlations: As seen in Table S21, there were no significant correlations between PANSS positive, negative and general scores and any thalamic nuclei volumes.

Voxel-based Morphometry: As seen in Figure S7 and Tables S7 and S8, the psychosis group had smaller volumes in a cluster with peaks in the bilateral mediodorsal nucleus, pulvinar and left ventrolateral nucleus.

PNC: Supplementary Analyses

Sensitivity Analysis: The matched PNC sub-sample did not show a significant main effect of group ($F(1,278)=3.729$, $p=.06$), or nuclei by group interaction ($F(4,1112)=2.255$, $p=.06$). As with the full PNC, this sub-sample showed no significant effect of group in the mediodorsal ($F(1,278)=.822$, $p=.37$), ventrolateral ($F(1,278)=.632$, $p=.43$), ventral anterior ($F(1,278)=2.762$, $p=.10$) or ventral posterolateral nuclei ($F(1,278)=2.396$, $p=.12$). Mean volumes and full statistical results for the main analysis and this one are presented in Tables S5 and S6.

Whole Thalamus effects: An examination of whole thalamus volumes found that the main effect of group was not significant in the PNC ($F(2,1387) = 2.195$, $p = .11$).

Hemisphere effects: The mediodorsal ($F(1,1387)=84.946$, $p<.001$), pulvinar ($F(1,1387)=149.194$, $p<.001$) and ventral posterolateral ($F(1,1387)=40.650$, $p<.001$) nuclei showed significantly lower volumes in the left hemisphere. There were no significant group by

hemisphere interactions in any nucleus. See Table S14 for mean volumes of each hemisphere and full statistical results.

Age effects: As seen in Figure S9, there was a significant main effect of age in all thalamic nuclei. The mediodorsal nucleus was negatively correlated with age; older youth showed smaller mediodorsal volume. All other thalamic nuclei were positively correlated with age; older youth showed larger volume. There were no age by group interactions in any thalamic nuclei. See Table S15 for full statistical results.

Sex effects: There was a significant main effect of sex in all thalamic nuclei, with females showing smaller volumes in all nuclei, after adjusting for age and ICV. There was no group by sex interaction in any of the nuclei. See Table S16 for full statistical results.

Voxel-based Morphometry: As seen in Figure S7 and Tables S9 and S10, psychosis spectrum youth had smaller volumes in a cluster with peaks in the bilateral anterior nucleus and left mediodorsal nucleus and pulvinar.

Thalamic Nuclei Volumes and Cognition: Supplementary Analyses

Psychosis cohort correlation with cognitive subscales: In exploratory analyses, we examined the correlation between the whole thalamus, thalamic nuclei and the SCIP sub-scales. Results are presented in Tables S17 and S19. None of the correlations were significant at a Bonferroni correct alpha of 0.0016.

PNC correlation with cognitive subscales: In exploratory analyses, we examined the correlation between the whole thalamus, thalamic nuclei and the CNB subscales. As presented in Tables S18 and S20, pulvinar volumes were significantly correlated with Executive Function ($R_{partial}$=.091, p<.001) and Complex Cognition ($R_{partial}$=.157, p<.001). No other correlations were significant at a Bonferroni corrected alpha of .0016.

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SUPPLEMENTAL TABLES

TABLE S1. Demographics of study participants in psychosis cohort, separated by psychotic disorder diagnosis.

	Healthy Individuals		Schizophrenia Spectrum Disorders		Psychotic Bipolar Disorder		Statistics			
	(n=179)		(n=199)		(n=94)		df	x^2/t/F	p	Contrasts
Gender (F:M)	73:106		65:134		50:44		2	11.34	.003	--
Ethnicity (W:AA:O)	124:46:9		130:63:6		75:11:8		4	15.90	.003	--
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**				
Age	29.2	10.2	29.6	11.4	31.1	12.2	2,469	0.94	.391	--
Education	15.5	2.1	13.3	2.2	14.1	2.0	2,440	44.19	<.001	HI > BD > SCZ
Parental Education	14.7	2.4	14.4	2.7	14.8	2.4	2,432	0.92	.400	--
Neuropsychological Functioning										
SCIP Composite z-score	0.12	0.65	-1.05	0.95	-0.64	0.91	2,455	91.78	<.001	HI > BD > SCZ
Estimated Premorbid IQ	111.1	11.2	99.7	15.7	106.5	13.2	2,457	31.76	<.001	HI > BD > SCZ
Clinical Characteristics										
Duration of Illness (years)	--	--	8.8	11.2	6.9	9.0	289	1.40	.163	--
PANSS Positive	--	--	17.6	8.1	15.1	9.3	285	2.32	.021	--
PANSS Negative	--	--	15.4	6.7	10.3	3.6	285	6.80	<.001	--
PANSS General	--	--	30.9	8.5	26.7	7.5	284	4.07	<.001	--
YMRS	--	--	4.9	6.8	9.0	12.9	277	-3.49	.001	--
APD Dose (in CPZ equivalents)	--	--	358.0	221.6	264.4	196.0	127	2.38	.019	--

Abbreviations: AA=African American; APD=Antipsychotic Drug; BD=Psychotic Bipolar Disorder; CPZ=Chlorpromazine; F=Female; HI=Healthy Individuals; M=Male; O=Other; PANSS=Positive and Negative Syndrome Scale; SCIP=Screen for Cognitive Impairment in Psychiatry; SCZ=Psychosis Spectrum Disorders; W=White; YMRS=Young Mania Rating Scale

TABLE S2. Demographics for the sub-set of youth from the Philadelphia Neurodevelopmental Cohort included in the sensitivity analysis.

	Typically Developing (n=133)		**Psychosis Spectrum** (n=150)		**Statistics** df	x^2/t/F	p
Gender (F:M)	63:70		75:75		1	0.20	.658
Ethnicity (W:AA:O)	61:52:20		54:78:18		2	4.73	.094
	Mean	**SD**	**Mean**	**SD**			
Age	14.9	2.9	15.0	2.6	281	-0.34	.731
Education	7.9	2.9	7.5	2.5	281	1.12	.262
Parental Education	14.2	2.4	13.6	2.3	279	2.02	.044
<u>Neuropsychological Functioning</u>							
CNB Composite z-score	0.04	0.47	-0.05	0.56	281	2.15	.032
WRAT Standard score	104.3	17.0	99.1	16.1	281	2.64	.009

Abbreviations: AA=African American; F=Female; M=Male; O=Other; W=White; WRAT=Wide Range Assessment Test

TABLE S3. Estimated mean volumes of thalamic nuclei in the psychosis cohort.

Thalamic Nucleus	Healthy Individuals		Psychosis		Statistics[a]				
	Mean (mm^3)	SE	Mean (mm^3)	SE	Cohen's f	% reduction[b]	df	F	p
Mediodorsal	2041	10.7	1988	8.3	0.182	2.60	1,465	15.52	<.001
Pulvinar	3391	18.7	3298	14.6	0.182	2.74	1,465	14.19	<.001
Ventrolateral	2892	15.9	2836	12.4	0.128	1.94	1,465	7.48	.006
Ventral Anterior	859	5.4	847	4.2	0.084	1.40	1,546	3.28	.071
Ventral Posterolateral	1621	9.2	1599	7.2	0.090	1.36	1,465	3.58	.059

[a] age, sex, project and ICV included as covariates

[b] % reduction is calculated relative to healthy individuals

TABLE S4. Estimated mean volumes of thalamic nuclei in the psychosis cohort, separated into schizophrenia spectrum and psychotic bipolar disorder.

Thalamic Nucleus	Healthy Individuals		Schizophrenia Spectrum		Psychotic Bipolar Disorder		Statistics[a]					
	Mean (mm^3)	SE	Mean (mm^3)	SE	Mean (mm^3)	SE	Cohen's f	% reduction in SZ[b]	% reduction in BP[b]	df	F	p
Mediodorsal	2041	10.7	1983	10.1	1998	15.0	0.188	2.84	2.11	2,464	8.066	<.001
Pulvinar	3390	18.6	3276	17.7	3344	26.1	0.207	3.36	1.36	2,464	9.928	<.001
Ventrolateral	2892	15.9	2837	15.1	2834	22.4	0.128	1.90	2.01	2,464	3.741	.024
Ventral Anterior	859	5.4	849	5.2	842	7.6	0.090	1.16	1.98	2,464	1.863	.156
Ventral Posterolateral	1621	9.2	1591	8.8	1614	13.0	0.110	1.85	0.43	2,464	2.881	.057

[a] age, sex, project and ICV included as covariates
[b] % reduction is calculated relative to healthy individuals

TABLE S5. Estimated mean volumes of thalamic nuclei in the Philadelphia Neurodevelopmental Cohort.

Thalamic Nucleus	Typically Developing (TD)		Psychosis Spectrum (PS)		Other Psychopathology (OP)		Statistics[a]					
	Mean (mm3)	SE	Mean (mm3)	SE	Mean (mm3)	SE	Cohen's f	% reduction in PS[b]	% reduction in OP[b]	df	F	p
Mediodorsal	2228	9.5	2210	9.4	2218	7.5	0.032	0.08	0.45	2,1387	.85	.429
Pulvinar	3518	17.4	3442	17.3	3498	13.7	0.084	2.16	0.57	2,1387	5.21	.006
Ventrolateral	3040	11.5	3027	11.4	3030	9.1	0.032	0.43	0.33	2,1387	.39	.681
Ventral Anterior	894	3.7	888	3.7	888	2.9	0.032	0.67	0.67	2,1387	.80	.448
Ventral Posterolateral	1769	8.8	1753	8.7	1767	6.9	0.045	0.90	0.11	2,1387	1.07	.343

[a] age, sex and ICV included as covariates

[b] % reduction is calculated relative to typically developing youth

TABLE S6. Estimated mean volumes of thalamic nuclei in the Philadelphia Neurodevelopmental Cohort sensitivity analysis.

Thalamic Nucleus	Typically Developing		Psychosis Spectrum		Statistics[a]				
	Mean (mm3)	SE	Mean (mm3)	SE	Cohen's f	% reduction[b]	df	F	p
Mediodorsal	2218	16.7	2198	15.7	0.055	0.90	1,278	.82	.365
Pulvinar	3515	29.9	3425	28.1	0.135	2.56	1,278	5.04	.026
Ventrolateral	3032	21.1	3010	19.8	0.045	0.73	1,278	.63	.427
Ventral Anterior	896	6.7	881	6.4	0.101	1.67	1,278	2.76	.098
Ventral Posterolateral	1776	16.1	1744	15.1	0.095	1.80	1,278	2.40	.123

[a] age, sex and ICV included as covariates
[b] % reduction is calculated relative to typically developing youth

TABLE S7. Peak coordinates from voxel-wise comparison of gray matter volume differences in Healthy > Psychosis groups comparison from psychosis cohort.

Region	Hemisphere	Cluster size	Z	Coordinates		
				x	y	z
Mediodorsal Nucleus	Bilateral	2179	6.1	0	-12	10
	Right		3.99	6	-22	12
Pulvinar	Right		4.97	14	-34	6
	Left		4.88	-14	-36	4
Ventrolateral Nucleus	Left		3.46	-15	-9	9

TABLE S8. Percentage overlap of significant cluster from the voxel-based morphometry analysis with thalamic nuclei in the psychosis cohort. Statistical parametric maps from the Healthy Individuals > Psychosis contrast were overlaid on the Krauth atlas of thalamic nuclei and the percentage overlap with each nucleus was calculated across statistical thresholds ranging from $p=10^{-3}$ to 10^{-5}.

	% of nucleus covered	
	Left	**Right**
Threshold $p=10^{-3}$		
Mediodorsal	84.5	92.9
Pulvinar	37.1	41.3
Ventrolateral	16.2	11.7
Ventral Anterior	1.4	0.0
Ventral Posterolateral	0.0	0.0
Threshold $p=10^{-4}$		
Mediodorsal	67.8	78.4
Pulvinar	6.5	19.5
Ventrolateral	1.4	1.9
Ventral Anterior	0.0	0.0
Ventral Posterolateral	0.0	0.0
Threshold $p=10^{-5}$		
Mediodorsal	49.8	60.6
Pulvinar	0.5	2.9
Ventrolateral	0.0	0.0
Ventral Anterior	0.0	0.0
Ventral Posterolateral	0.0	0.0

TABLE S9. Peak coordinates from voxel-wise comparison of gray matter volume differences in Typically Developing > Psychosis Spectrum youth from the Philadelphia Neurodevelopmental Cohort.

Region	**Hemisphere**	**Cluster Size**	**Z**	**Coordinates**		
				x	y	z
Anterior Nucleus	Right	131	4.25	10	-6	12
	Left	569	4.03	-9	-9	14
Mediodorsal Nucleus	Left		4.24	-8	-20	10
Pulvinar	Left		4.06	-8	-27	12

TABLE S10. Percentage overlap of significant clusters from the voxel-based morphometry analysis with thalamic nuclei in the Philadelphia Neurodevelopmental Cohort (PNC). Statistical parametric maps from the Typically Developing > Psychosis Spectrum contrast were overlaid on the Krauth atlas of thalamic nuclei and the percentage overlap with each nucleus was calculated across statistical thresholds ranging from $p=10^{-3}$ to 10^{-4}. In the PNC, no voxels were significant at $p=10^{-5}$.

	% of nucleus covered	
	Left	**Right**
Threshold p=.001		
Mediodorsal	34.3	1.4
Pulvinar	10.7	0.0
Ventrolateral	22.6	21.7
Ventral Anterior	0.7	5.5
Ventral Posterolateral	14.9	0.7
Threshold p=.0001		
Mediodorsal	15.9	0.0
Pulvinar	2.2	0.0
Ventrolateral	7.1	7.1
Ventral Anterior	0.0	1.4
Ventral Posterolateral	6.4	0.0

TABLE S11. Mean Volumes by hemisphere, and group x hemisphere statistics in the psychosis cohort.

Thalamic Nucleus	Healthy Individuals				Psychosis				Statistics[a]		
	Left		Right		Left		Right				
	Mean (mm^3)	SE	Mean (mm^3)	SE	Mean (mm^3)	SE	Mean (mm^3)	SE	df	F	p
Mediodorsal	1022	6.1	1019	5.6	999	4.8	989	4.3	1,465	1.14	.286
Pulvinar	1695	10.8	1695	9.7	1647	8.4	1651	7.6	1,465	0.12	.730
Ventrolateral	1461	8.5	1431	7.9	1430	6.7	1406	6.2	1,465	0.86	.355
Ventral Anterior	434	3.1	425	2.8	426	2.4	420	2.2	1,465	0.73	.393
Ventral Posterolateral	848	5.1	773	4.7	835	4.0	764	3.7	1,465	0.54	.464

[a] age, sex, project and ICV included as covariates

TABLE S12. Age effects and group by age interactions in the psychosis cohort.

	Statistics	
	$R_{partial}$[a]	p
Main Effect of Age		
Mediodorsal	-.272	<.001
Pulvinar	-.445	<.001
Ventrolateral	-.194	<.001
Ventral Anterior	-.176	<.001
Ventral Posterolateral	-.091	.050
Age by Group Interaction		
Mediodorsal	.000	.998
Pulvinar	.035	.455
Ventrolateral	-.008	.870
Ventral Anterior	.022	.636
Ventral Posterolateral	-.027	.565

[a] sex, project and ICV included as covariates

TABLE S13. Sex effects and group by sex interactions in the psychosis cohort.

	Statistics[a]		
	F	**df**	**p**
Main Effect of Sex			
Mediodorsal	9.582	1,464	.002
Pulvinar	5.591	1,464	.018
Ventrolateral	25.888	1,464	<.001
Ventral Anterior	23.889	1,464	<.001
Ventral Posterolateral	21.044	1,464	<.001
Sex by Group Interaction			
Mediodorsal	0.102	1,464	.750
Pulvinar	2.779	1,464	.096
Ventrolateral	0.157	1,464	.692
Ventral Anterior	0.557	1,464	.456
Ventral Posterolateral	0.209	1,464	.648

[a] age, project and ICV included as covariates

TABLE S14. Mean Volumes by hemisphere, and group x hemisphere statistics in the Philadelphia Neurodevelopmental Cohort.

Thalamic Nucleus	TD				PS				OP				Statistics[a]		
	Left		Right		Left		Right		Left		Right				
	Mean (mm^3)	SE	Mean (mm^3)	SE	Mean (mm^3)	SE	Mean (mm^3)	SE	Mean (mm^3)	SE	Mean (mm^3)	SE	df	F	p
Mediodorsal	1085	5.0	1142	5.7	1074	4.3	1136	5.7	1077	3.9	1141	4.5	2,1387	0.61	.543
Pulvinar	1534	7.6	1984	12.8	1499	7.6	1943	12.7	1523	6.0	1976	10.1	2,1387	0.15	.860
Ventrolateral	1516	6.1	1524	6.1	1509	6.0	1518	6.1	1512	4.8	1518	4.8	2,1387	0.12	.890
Ventral Anterior	457	2.1	437	1.9	457	2.1	431	1.9	455	1.7	433	1.5	2,1387	3.53	.030
Ventral Posterolateral	845	4.3	924	5.4	832	4.3	921	5.4	845	3.4	922	4.3	2,1387	2.82	.060

[a] age, sex and ICV included as covariates

TABLE S15. Age effects and group by age interactions in the Philadelphia Neurodevelopmental Cohort.

	Statistics[a]			
	$R_{partial}$	**p**	**$R_{partial}$**	**p**
Main Effect of Age				
Mediodorsal	-.055	.042	--	--
Pulvinar	.118	<.001	--	--
Ventrolateral	.241	<.001	--	--
Ventral Anterior	.126	<.001	--	--
Ventral Posterolateral	.351	<.011	--	--
Age by Group Interactions				
	Typically Developing by Psychosis Spectrum		Typically Developing by Other Psychopathologies	
Mediodorsal	-.040	.136	-.029	.272
Pulvinar	.008	.752	.013	.639
Ventrolateral	-.009	.728	-.010	.712
Ventral Anterior	-.019	.850	-.005	.482
Ventral Posterolateral	-.026	.336	-.033	.224

[a] sex and ICV included as covariates

TABLE S16. Sex effects and group by sex interactions in the Philadelphia Neurodevelopmental Cohort.

	Statistics[a]		
	F	**df**	**p**
Main Effect of Sex			
Mediodorsal	15.341	1,1385	.042
Pulvinar	11.081	1,1385	<.001
Ventrolateral	23.885	1,1385	<.001
Ventral Anterior	24.967	1,1385	<.001
Ventral Posterolateral	21.685	1,1385	<.001
Sex by Group Interaction			
Mediodorsal	1.730	2,1385	.178
Pulvinar	0.400	2,1385	.670
Ventrolateral	0.570	2,1385	.565
Ventral Anterior	0.059	2,1385	.943
Ventral Posterolateral	0.277	2,1385	.758

[a] age and ICV included as covariates

TABLE S17. Partial correlation coefficients from regression of thalamic nuclei volumes and Screen for Cognitive Impairment in Psychiatry (SCIP) sub-scales in the psychosis cohort.

	Pulvinar		Mediodorsal		Ventrolateral		Ventral Anterior		Ventral Posterolateral	
	$R_{partial}$[a]	p	$R_{partial}$[a]	p	$R_{partial}$[a]	p	$R_{partial}$[a]	p	$R_{partial}$[a]	p
SCIP composite	.111	.019	.087	.063	.047	.322	.006	.895	.065	.166
Working Memory	.091	.051	.093	.047	.111	.017	.060	.202	.101	.030
Processing Speed	.079	.093	.035	.456	-.026	.575	-.054	.256	.045	.338
Immediate Verbal Learning	.031	.509	.069	.143	.006	.900	.080	.087	.022	.646
Delayed Verbal Learning	.060	.200	.046	.327	-.039	.402	-.030	.520	-.016	.727
Verbal Fluency	.109	.021	.045	.338	.100	.033	-.043	.363	.064	.170

[a] adjusted for group; age, sex, project and ICV included as covariates

TABLE S18. Partial correlation coefficients from regression of thalamic nuclei volumes and Penn Computerized Neurocognitive Battery subscales (CNB) in the Philadelphia Neurodevelopmental Cohort.

	Pulvinar		Mediodorsal		Ventrolateral		Ventral Anterior		Ventral Posterolateral	
	$R_{partial}$[a]	p	$R_{partial}$[a]	p	$R_{partial}$[a]	p	$R_{partial}$[a]	p	$R_{partial}$[a]	p
CNB Composite	.121	<.001	.035	.193	-.024	.370	-.019	.486	-.007	.799
Executive Function	.091	<.001	.032	.227	-.020	.450	.004	.871	-.006	.817
Complex Cognition	.157	<.001	.051	.058	.006	.826	.018	.501	.007	.800
Episodic Memory	.051	.060	.017	.516	-.018	.826	-.018	.495	.010	.720
Social Cognition	.013	.626	-.016	.561	-.035	.190	-.053	.046	-.033	.214
Sensorimotor Ability	-.047	.080	-.020	.463	-.051	.059	-.028	.304	-.059	.028

[a] adjusted for group; age, sex, and ICV included as covariates

TABLE S19. Partial correlation coefficients from regression of whole thalamus volumes and Screen for Cognitive Impairment in Psychiatry (SCIP) sub-scales in the psychosis cohort.

	$R_{partial}$[a]	p
SCIP Composite	.080	.089
Working Memory	.106	.024
Processing Speed	.035	.463
Intermediate Verbal Learning	.096	.040
Delayed Verbal Learning	.023	.619
Verbal Fluency	.005	.915

[a] adjusted for group; age, sex, and ICV included as covariates

TABLE S20. Partial correlation coefficients from regression of whole thalamus volumes and Penn Computerized Neurocognitive Battery (CNB) subscales in the Philadelphia Neurodevelopmental Cohort.

	$R_{partial}$ [a]	p
CNB Composite	.048	.072
Executive Function	.042	.114
Complex Cognition	.079	.003
Episodic Memory	.021	.441
Social Cognition	-.020	.467
Sensorimotor Ability	-.054	.043

[a] adjusted for group; age, sex, and ICV included as covariates

TABLE S21. Partial correlation between thalamic nuclei and clinical measures (Positive and Negative Syndrome Scale [PANSS] and Young Mania Rating Scale [YMRS]) in the psychosis cohort.

	Mediodorsal		Pulvinar		Ventrolateral		Ventral Anterior		Ventral Posterolateral	
	$R_{partial}$[a]	p	$R_{partial}$[a]	p	$R_{parital}$[a]	p	$R_{partial}$[a]	p	$R_{partial}$[a]	p
PANSS Positive	-.048	.418	-.058	.329	-.060	.315	-.061	.304	-.024	.687
PANSS Negative	.014	.817	.009	.874	.-.025	.674	-.009	.886	-.013	.830
PANSS General	-.087	.144	-.028	.642	-.045	.455	-.062	.296	-.022	.709
YMRS	-.044	.469	-.018	.769	-.006	.921	-.010	.870	.052	.387

[a] adjusted for group; age, sex, ICV and project included as covariates

SUPPLEMENTAL FIGURES

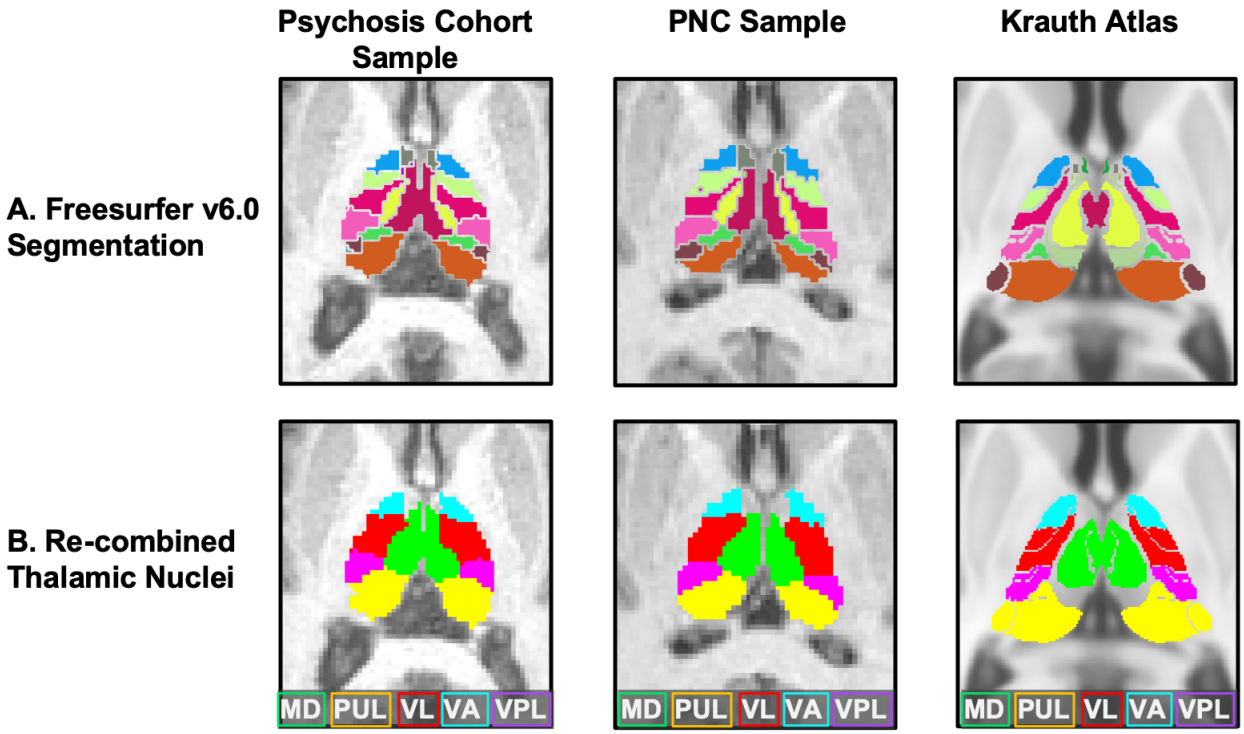

FIGURE S1. A. Examples of segmentation based on FreeSurfer Version 6 thalamus module run on a sample individual from the psychosis cohort, Philadelphia Neurodevelopmental Cohort and a schematic of the Krauth atlas (in MNI space), to allow comparison against a histological atlas and B. Examples of how we combined thalamic nuclei to create the 5 nuclei examined in this study and the Krauth atlas combinations in MNI space for comparison. The thalamic nuclei created were as follows: 1) the mediodorsal nucleus (MD) composed of the bilateral MDm and MDl subdivisions; 2) the pulvinar nucleus (PUL) composed of the bilateral PuL, PuI, PuA and PuM subdivisions; 3) the ventrolateral nucleus (VL) composed of the bilateral VLa and VLp subdivisions; 4) the ventral anterior (VA) nucleus composed of the bilateral VA and VAmc subdivisions and 5) the ventral posterolateral nucleus (VPL) composed of the bilateral VPL subdivisions.

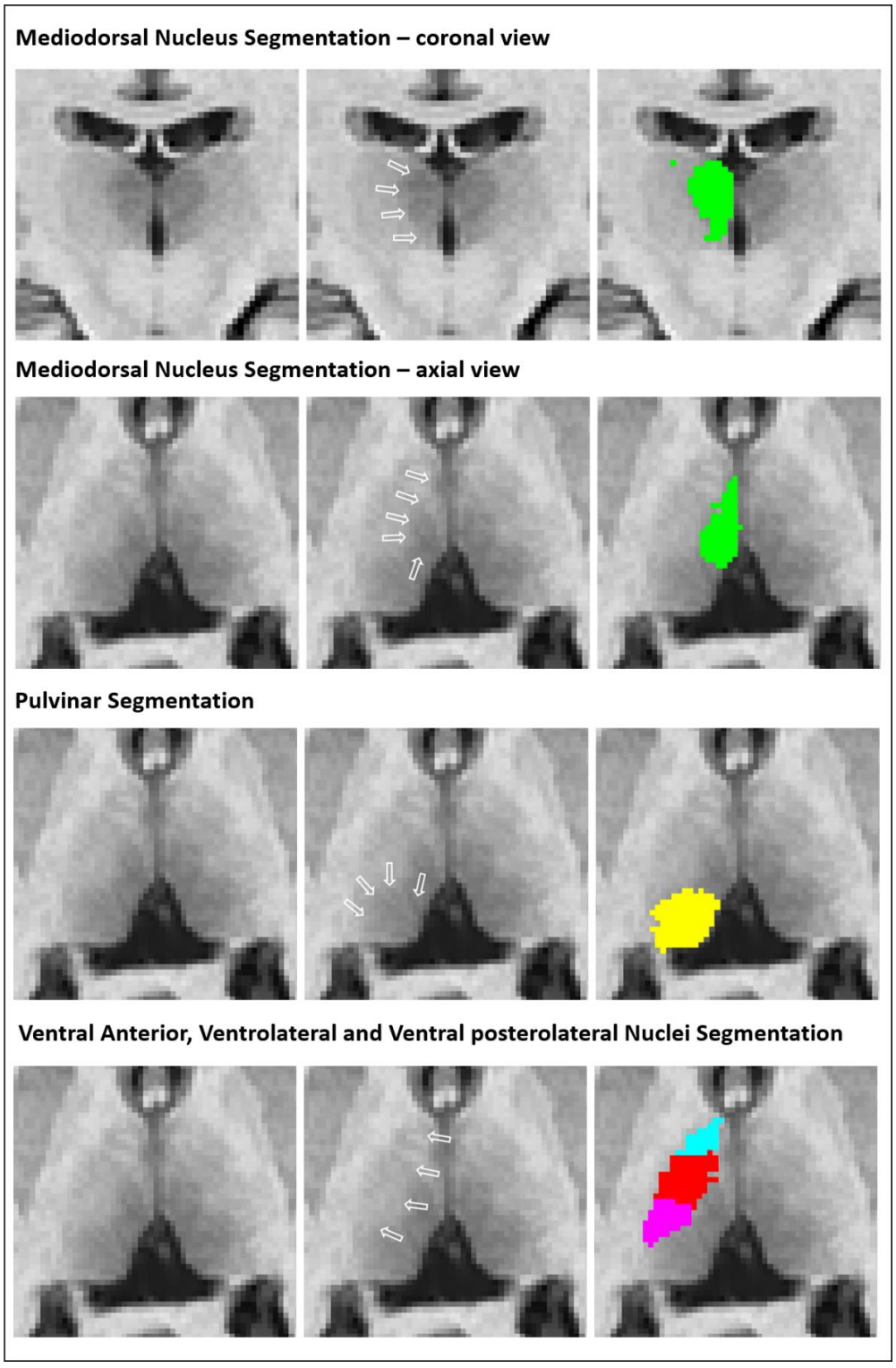

FIGURE S2. An example of the FreeSurfer segmentation for the mediodorsal nucleus, pulvinar, ventral anterior, ventrolateral and ventral posterolateral nuclei on Scan Sequence 1 T1 images in the Psychosis Cohort. White arrows highlight the contrast visible for the mediodorsal and pulvinar nuclei.

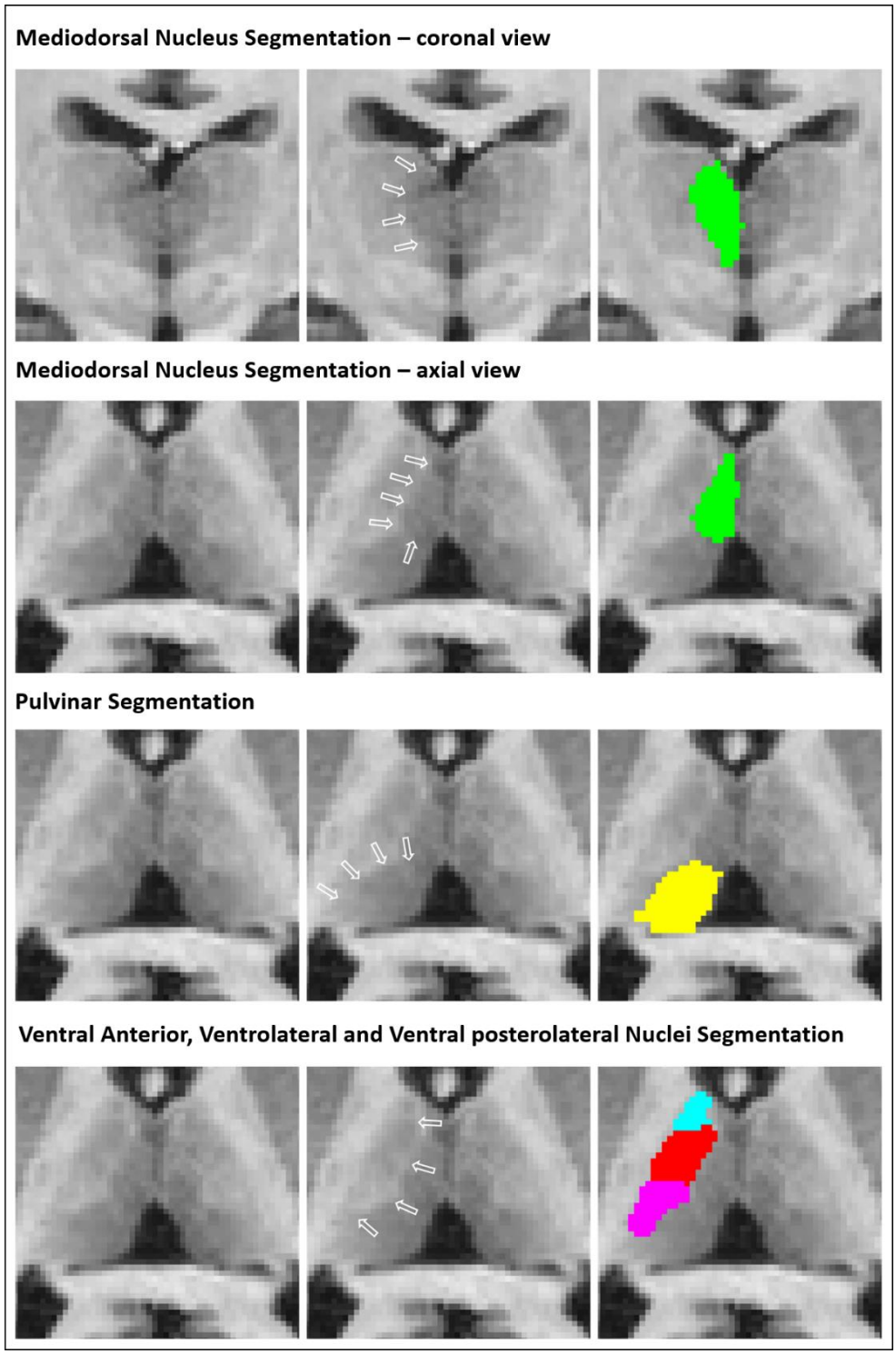

FIGURE S3. An example of the FreeSurfer segmentation for the mediodorsal nucleus, pulvinar, ventral anterior, ventrolateral and ventral posterolateral nuclei on Scan Sequence 2 T1 images in the Psychosis Cohort. White arrows highlight the contrast visible for the mediodorsal and pulvinar nuclei.

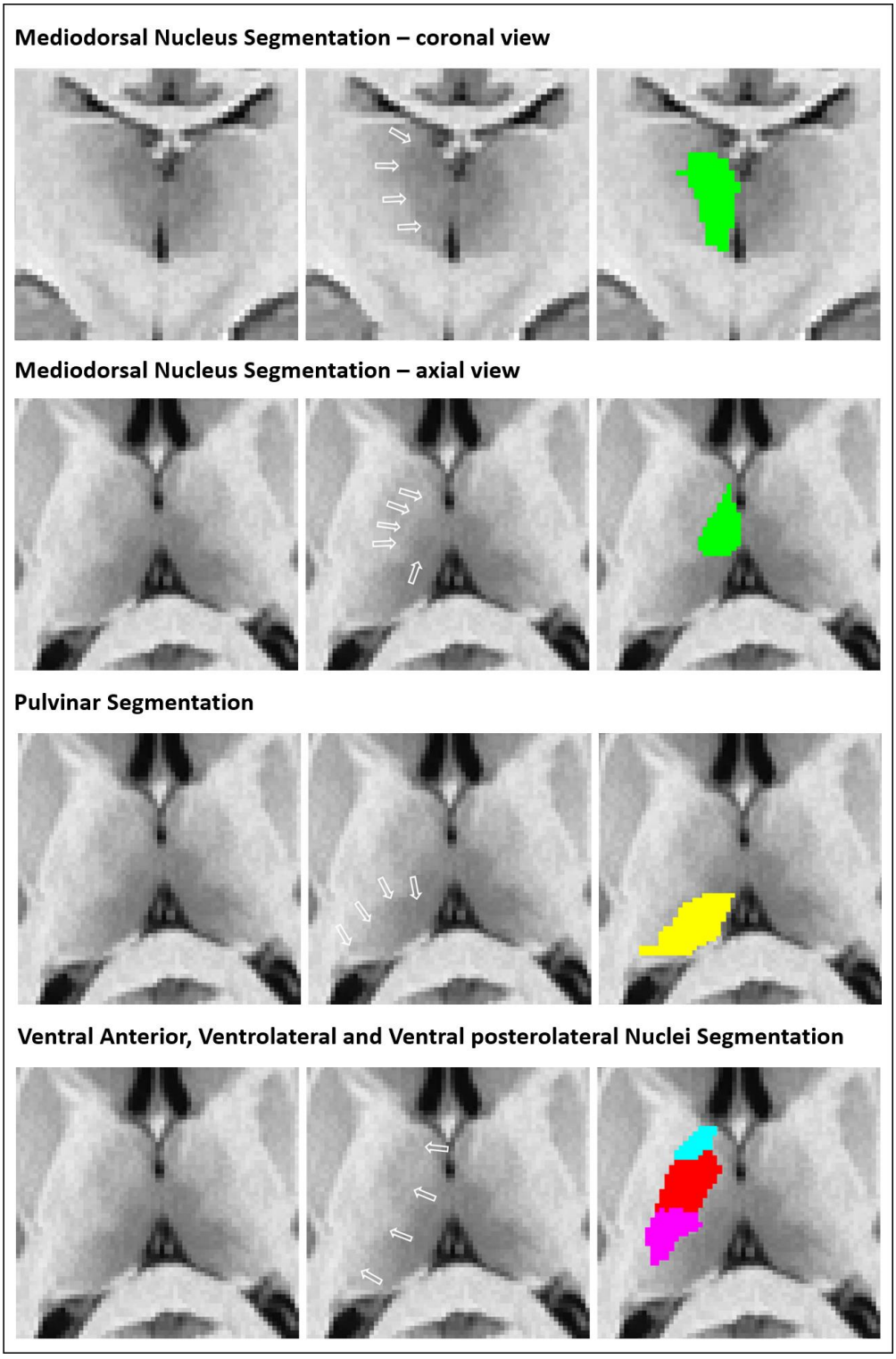

FIGURE S4. An example of the FreeSurfer segmentation for the mediodorsal nucleus, pulvinar, ventral anterior, ventrolateral and ventral posterolateral nuclei on T1 images in the Philadelphia Neurodevelopmental Cohort. White arrows highlight the contrast visible for the mediodorsal and pulvinar nuclei.

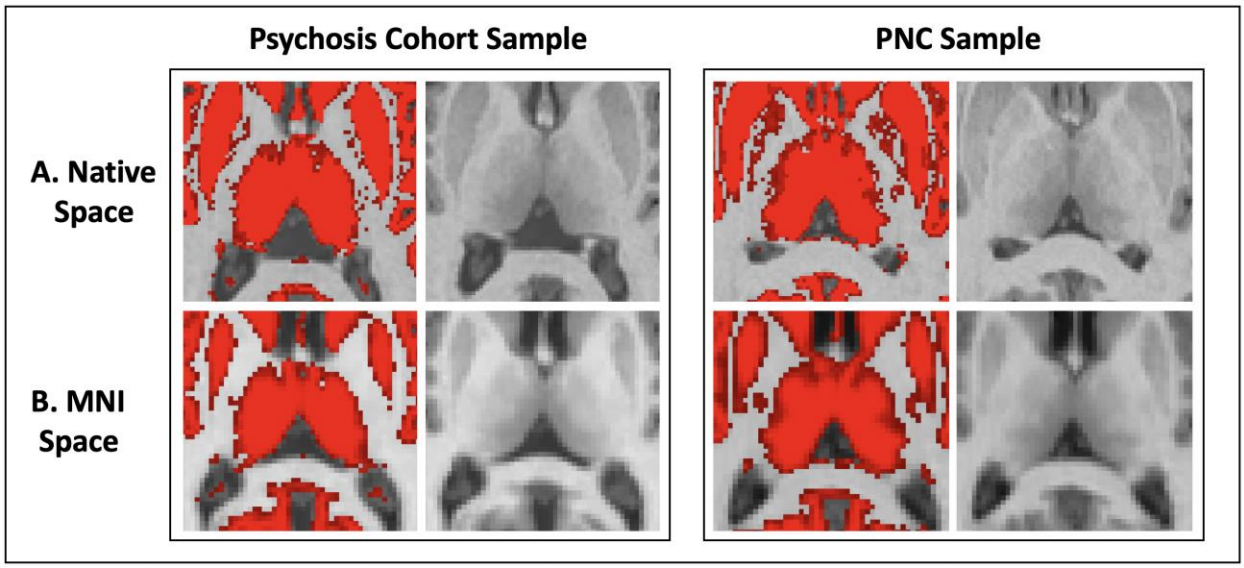

FIGURE S5. Examples of CAT12 grey matter segmentation results (in red) and corresponding T1 image from an individual in the psychosis cohort and in the Philadelphia Neurodevelopmental Cohort presented in A. Native space (individual subject space) and B. Montreal Neurological Institute (MNI) space.

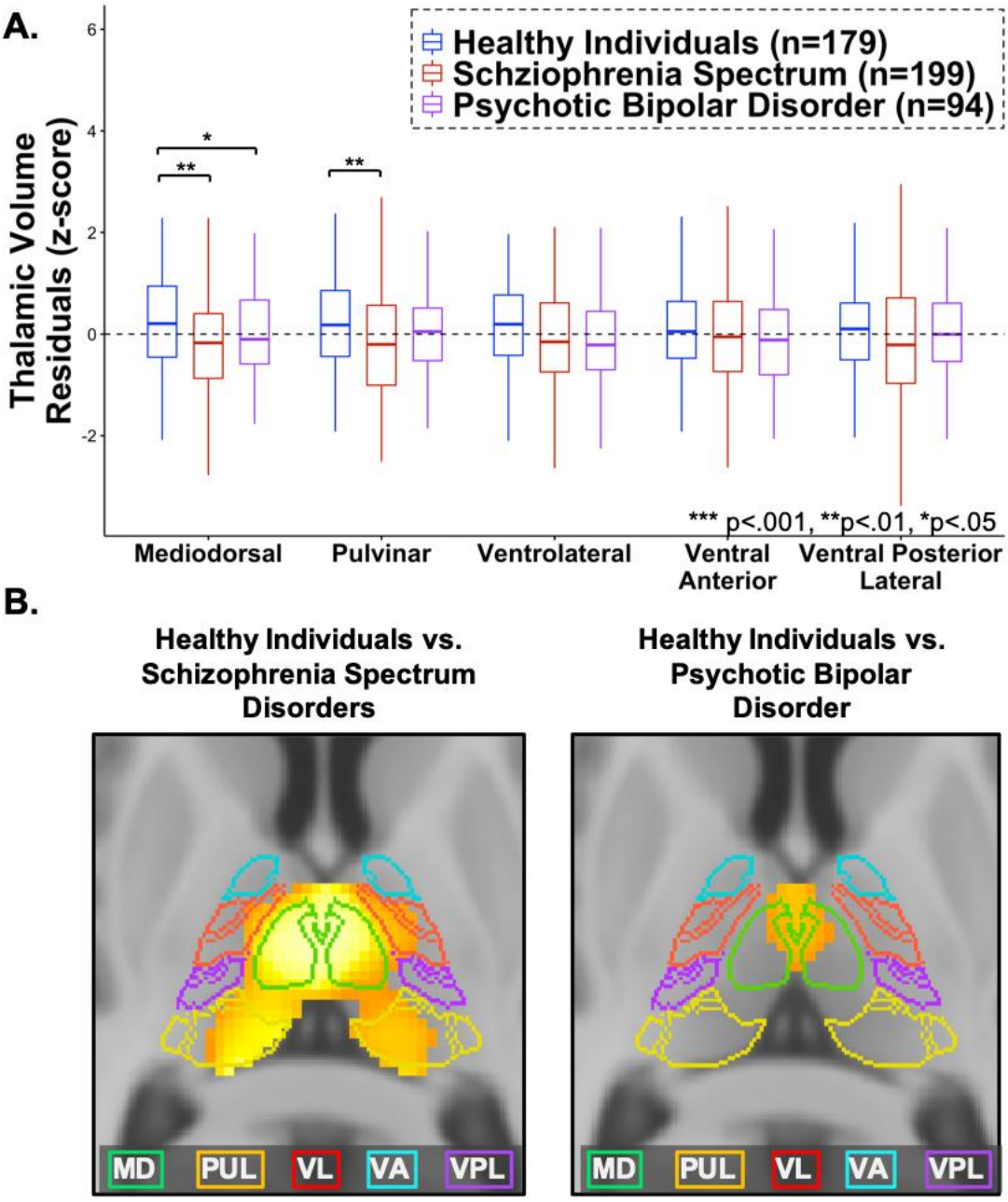

FIGURE S6. Thalamic nuclei volumes in healthy individuals, individuals with a schizophrenia spectrum diagnosis, and psychotic bipolar disorder. A. Standardized thalamic nuclei volumes from the FreeSurfer analysis. B. Voxel-wise analysis (VBM) results thresholded at voxel-wise threshold of p<.001 (uncorrected), p<.05 FWE cluster corrected.

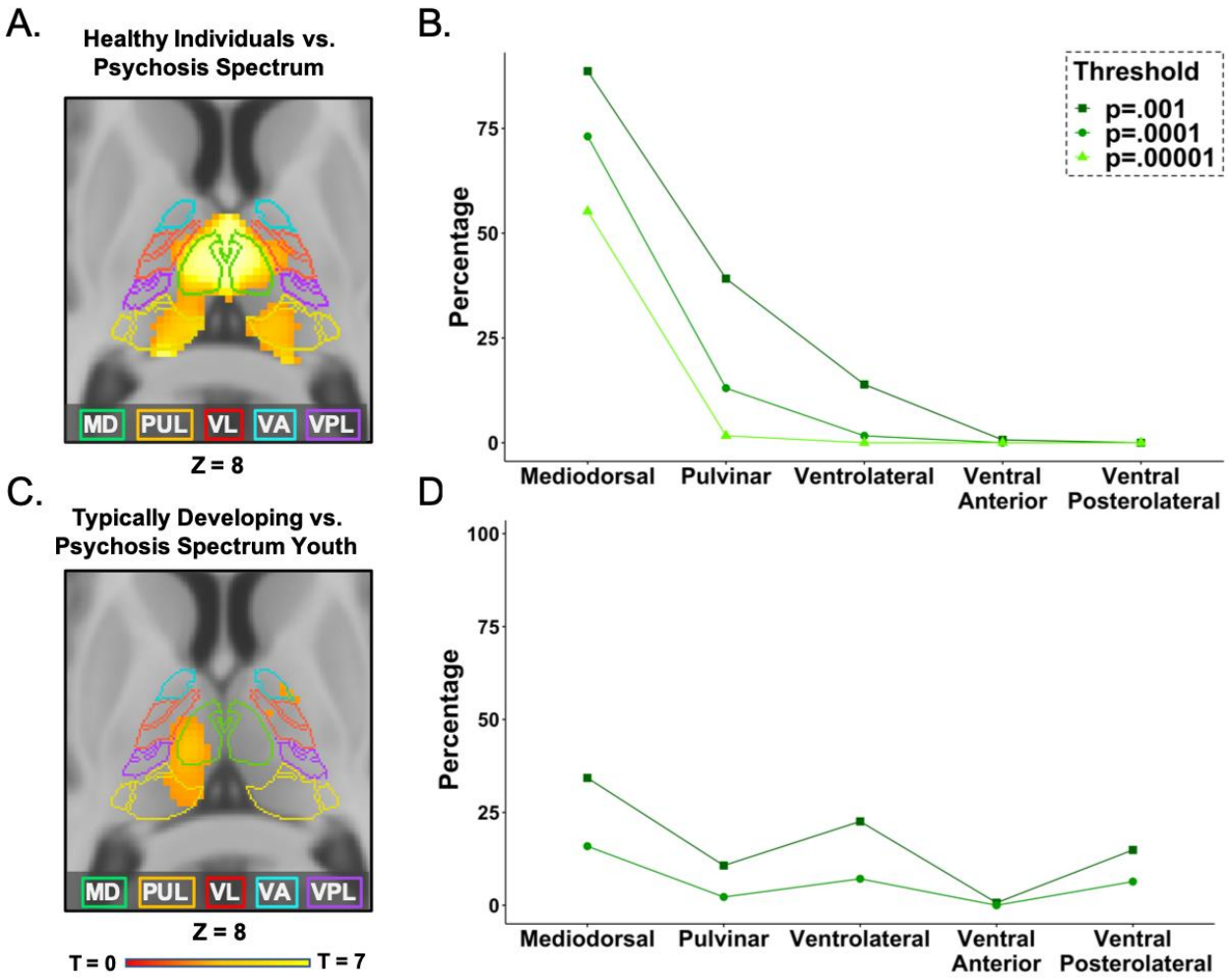

FIGURE S7. A. Voxel-wise voxel-based morphometry (VBM) analysis in the psychosis cohort. B. Percentage of thalamic nuclei covered by the cluster showing volume reduction in psychosis at different p-thresholds in the psychosis cohort, averaged across left and right hemispheres. C. Voxel-wise VBM analysis in the Philadelphia Neurodevelopmental Cohort (PNC). D. Percentage of thalamic nuclei covered by clusters showing volume reduction in the psychosis spectrum youth at different p-thresholds in the PNC, restricted to the left hemisphere.

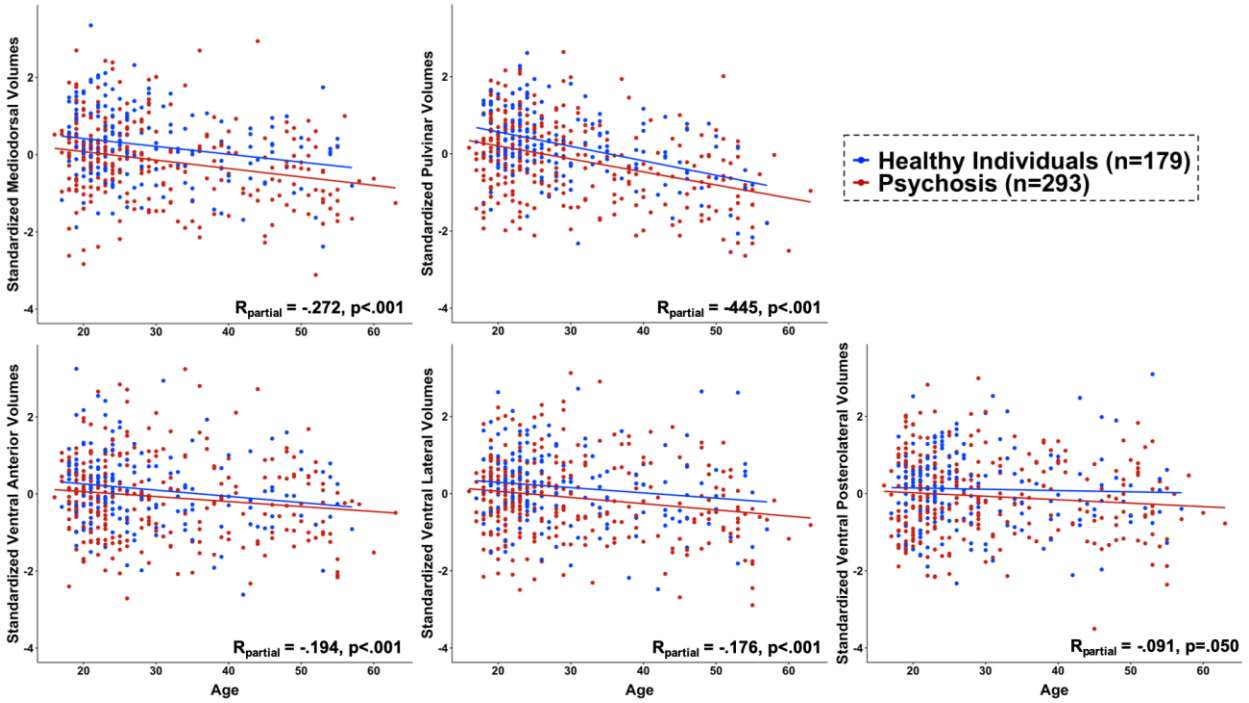

FIGURE S8. Association between age and nuclei volumes by group in the psychosis cohort.

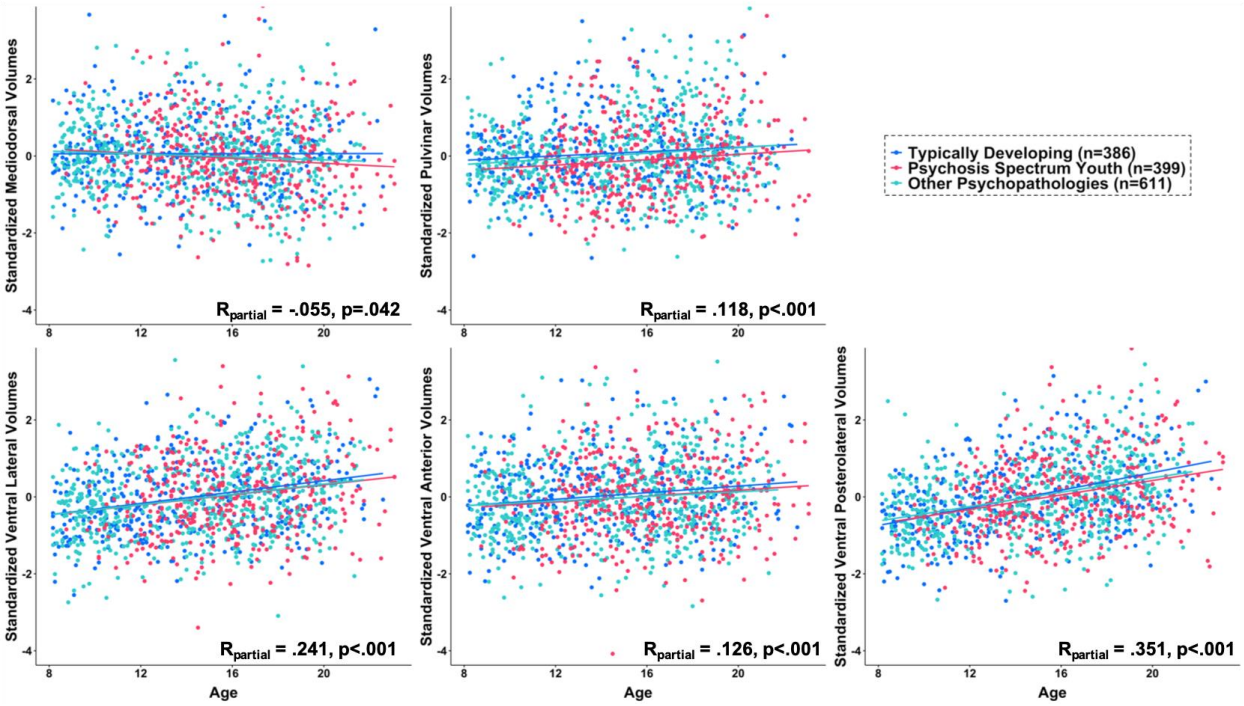

FIGURE S9. Association between age and nuclei volumes by group in the Philadelphia Neurodevelopmental Cohort.