Supplemental material:
Improvement in prefrontal thalamic connectivity during the early course of the illness in recent onset psychosis: A 12 month longitudinal follow up resting state fMRI study.

Contents

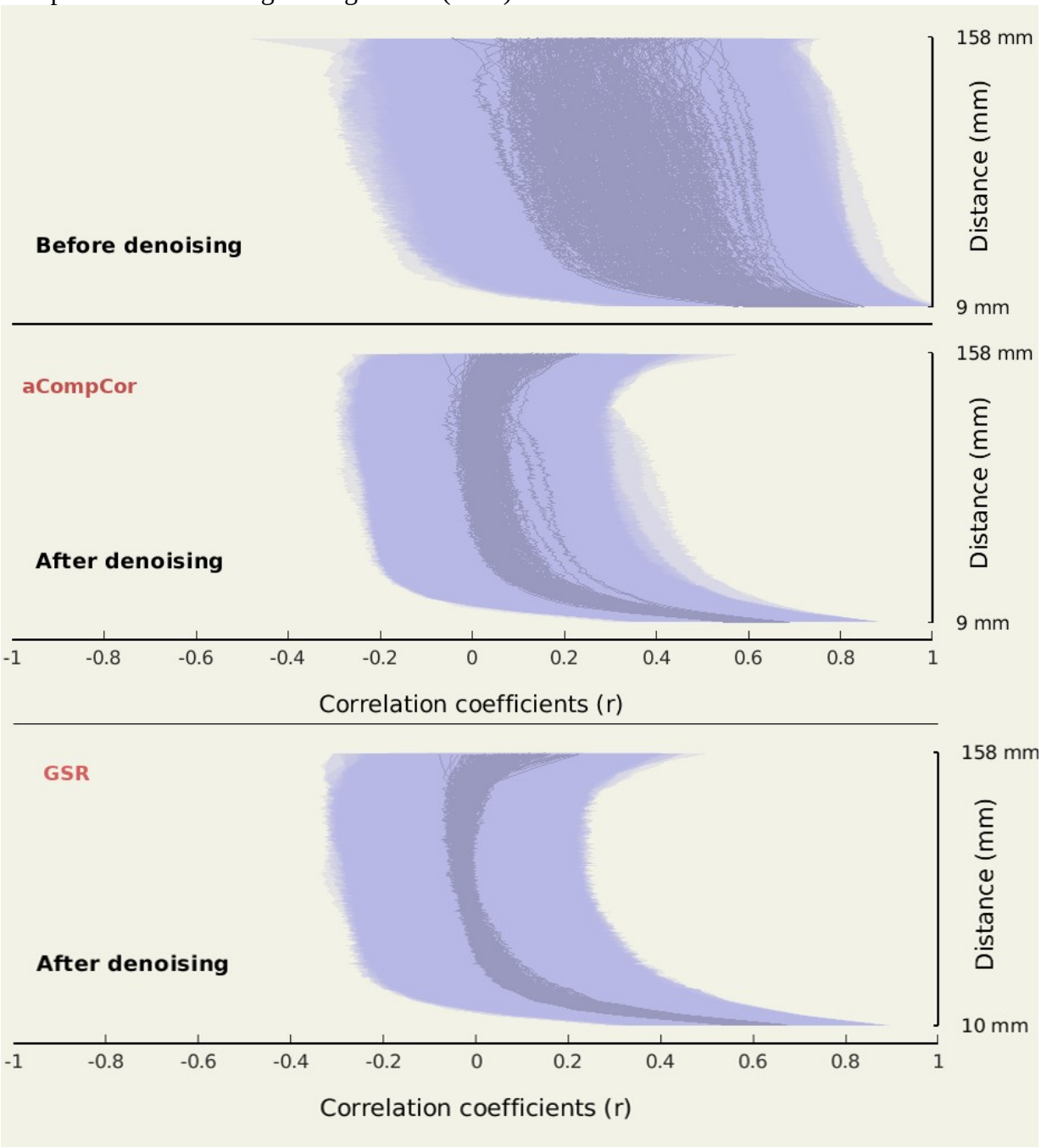
S1: Between groups comparison in motion parameters:

	ROP	HC	Statistic	*p*
N (%) excluded by mean FD > 0.9	5 (4%)	0	X-sq(1)=3.545	0.060
N excluded by scrubbing > 50% volumes	0	0	-	-
tSNR (SD) ‡	179.657 (58.198)	193.695 (50.908)	T(199.02) = 1.858	0.065
Average % vols scrubbed †	10.774 (13.028)	5.563 (10.218)	T(209) =-3.117 (11.9)	0.002
Mean FD (SD) *†	0.190 (0.074)	0.162 (0.049)	T(209)=-3.111	0.002

* Mean FD computed after excluding scrubbed volumes
† Computed after removing excessive motion subjects according to mean FD displacement > 0.9.
‡ Computed from the normalized functional images before the denoising process

ROP: Recent-onset psychosis; HC: Healthy controls; tSNR: Temporal signal to noise ratio. FD = Frame-wise displacement computed using the following formula $FD=\max\left(\sqrt{dx^2+dy^2+dz^2}\right)$, where dx, dy and dz represent the displacement in mm in the three axes of six reference voxels placed at the center of the default MNI brain's bounding box.

S2: Scatter plot of functional correlations and distance between voxels for two denoising strategies: aCompCor and Global Signal Regression (GSR)



Top plot shows functional correlations (Pearson coefficient) and distance between voxels in the brain before the denoising step. Middle plot shows the same scatter plot after denoising using aCompCor strategy (ie: regressing out 5 WM components, 5 CSF components, the realignment parameters and its first and second derivatives and volumes with excessive motion and its first derivative). Bottom plot shows the same plot after denoising using Global Signal Regression (GSR) strategy (ie: regressing out global signal, the realignment parameters and its first and second derivatives and volumes with excessive motion and its first derivative).

S3: Additional socio-demographic and clinical-characteristics

S3a: Comparison between recent-onset subjects with and without follow-up images.

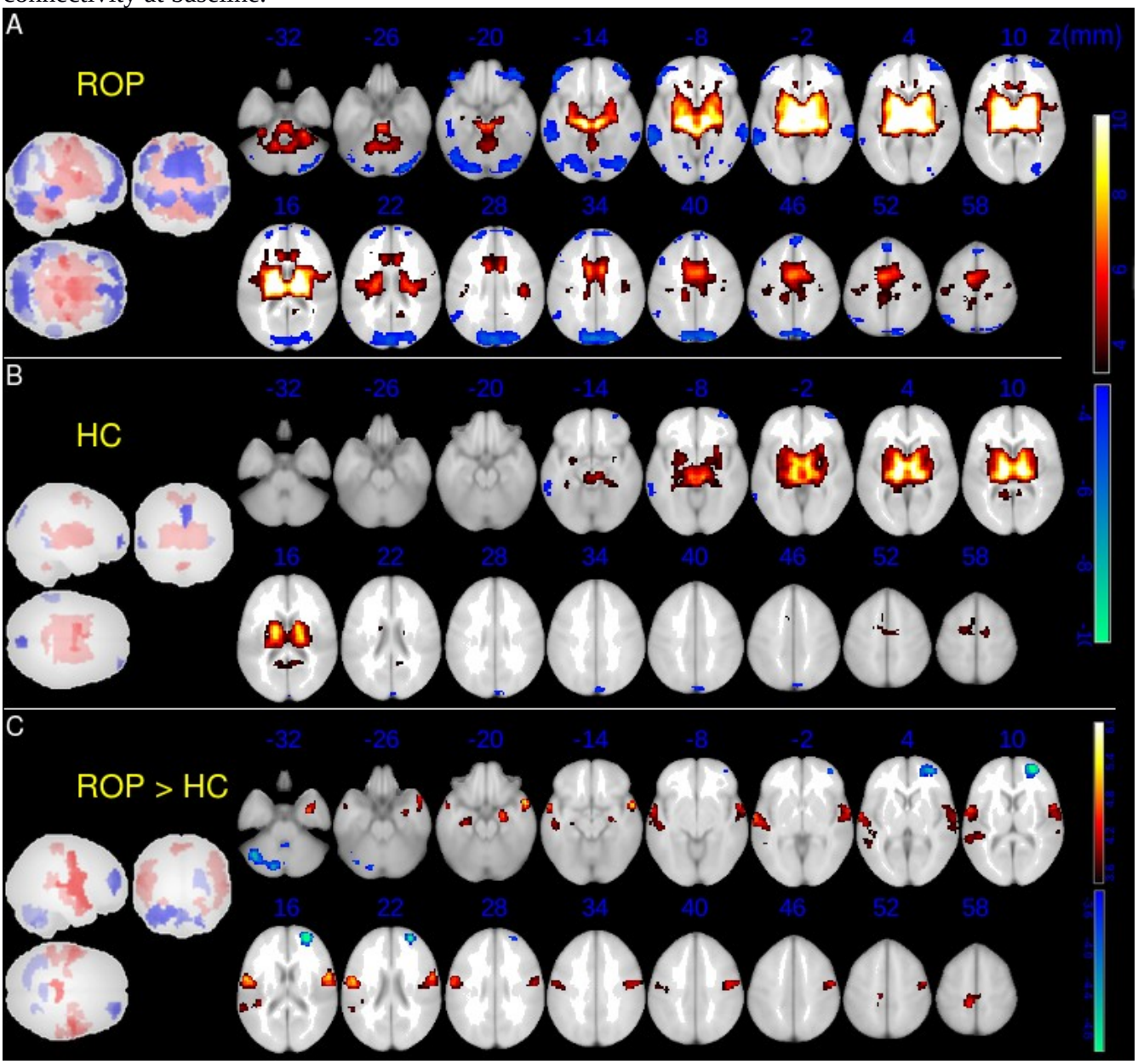
	ROP without follow-up images	**ROP with follow-up images**	**Stats**	**P value**
n	82	42		
Mean age at baseline scan (SD)	20.0 (4.3)	19.4 (3.5)	T(99.9)=0.896	0.372
Sex (% male)	76.8%	64.3%	X-sq(1)=1.611	0.204
Ethnicity (% Caucasian)	70.7%	69.0%	X-sq(1)~=0	~=1
Handedness (% right)	96.3%	87.5%	T(20.8)=0.945	0.355
Parental education, years (SD)	15.0 (2.6)	14.2 (2.9)	T(26.8)=0.898	0.377
GAF at baseline (SD)	55.2 (13.0)	44.2 (17.6)	T(19.2)=1.358	0.191
BPRS total at baseline, mean (SD)	42.1 (10.3)	42.0 (10.5)	T(83.9)=0.065	0.948
SAPS total at baseline, mean (SD)	4.0 (3.5)	3.9 (3.8)	T(78.7)=-0.048	0.962
SANS total at baseline, mean (SD)	9.5 (4.2)	9.6 (4.0)	T(87.2)=-0.193	0.848
Affective psychosis[1] (%)	20.3%	23.8%	X-sq(1)=0.049	0.825
DUP, days (SD)	184.3 (148.1)	181.5 (124.8)	T(96.8)=0.109	0.913
Time since psychosis onset: days (SD)	139.8 (92.8)	122.8 (92.3)	T(83.2)=0.969	0.336

ROP: Recent-onset psychosis; HC: Healthy controls; GAF: Global assessment of functioning; BPRS: Brief psychiatric rating scale; SAPS: Scale for the assessment of positive symptoms; SANS: Scale for the assessment of negative symptoms.

S3b: Clinical diagnostics at baseline from baseline subjects and follow-up subjects.

Diagnostic	Baseline subjects n=124 n (%)	Follow-up subjects n=42 n (%)
Schizophrenia	30 (24.2)	10 (24.0)
Schizoaffective	17 (13.7)	3 (7.1)
Schizophreniform	28 (22.6)	12 (28.6)
Psychosis NOS	21 (16.9)	7 (16.7)
Bipolar disorder with psychotic features	22 (17.7)	7 (16.7)
Major depressive disorder with psychotic features	5 (4.0)	3 (7.1)
Other	1 (0.8)	0

S4: Secondary analysis using global signal regression (GSR) instead of the default aCompCor strategy: significant clusters showing within group patterns and between group differences in thalamic connectivity at baseline.



ROP: Recent-onset psychosis; HC: Healthy controls. Within group thalamic connectivity at baseline in ROP **(A)** and controls **(B).** Red range color scale displays positive correlation with thalamic activity. Blue range color scale represents negative correlations with thalamic activity. **C**: Between-group significant clusters in thalamic connectivity. Red range scale displays higher thalamic connectivity in ROP compared to controls. Blue range scale displays lower connectivity in ROP compared to controls. All results are corrected using an initial cluster-defining threshold of $p<0.001$ at voxel-level and a subsequent cluster-extent FDR correction at $p<0.05$.

A certain number of studies have stated that GSR adequately corrects for movement-induced positive correlations but might not be equally effective in negative correlations. On the other side, aCompCor is thought to correct for overestimation of spurious positive correlations induced by movement likewise GSR, and additionally, correct more rigorously for spurious anticorrelations

(Muschelli *et al.*, 2014). According to the literature in the field, we expected negative correlations between the thalamus and cortical regions (Anticevic *et al.*, 2014), and thus, we chose the technique that is thought to better correct for spurious negative correlations. That being said, the results in our study, using both techniques, are very similar (see figure 1 and Supplementary Data S3). Although GSR seems to result in larger clusters of negative thalamic correlation in prefrontal cortex and cerebellum in the group of ROP (S3, top figure), the resulting between group comparisons does not differ enormously (S3, bottom figure and Figure 1, bottom). All the resulting clusters of decreased thalamic connectivity found in GSR are also present using the aCompCor strategy, and additionally, a cluster involving decreased connectivity in the left anterior cingulate gyrus emerges. As aCompCor has shown a better correction for movement-induced spurious negative correlations, this finding is unlikely to correspond to movement artifacts. On the other side, positive correlations in single group analysis do not differ importantly in the size of the resulting clusters using GSR or aCompCor. However, in the between group analysis, although the pattern of increased thalamic connectivity on somatosensory and temporal regions is very similar between both techniques, results using aCompCor reflect larger clusters. Due to the similar efficacy in correcting movement-induced positive correlations between GSR and aCompCor, it is not probable that this finding corresponds to an overestimation of between-group differences.

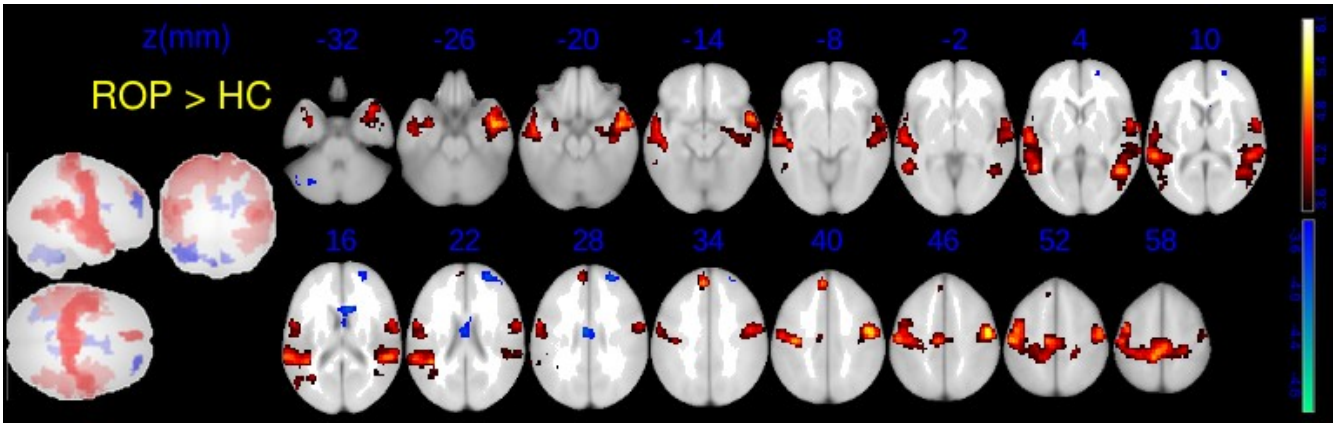
References:

Anticevic A, Cole MW, Repovs G, Murray JD, Brumbaugh MS, Winkler AM, Savic A, Krystal JH, Pearlson GD, Glahn DC (2014) Characterizing thalamo-cortical disturbances in schizophrenia and bipolar illness. *Cerebral Cortex (New York, N.Y.: 1991)* 24, 3116–3130.

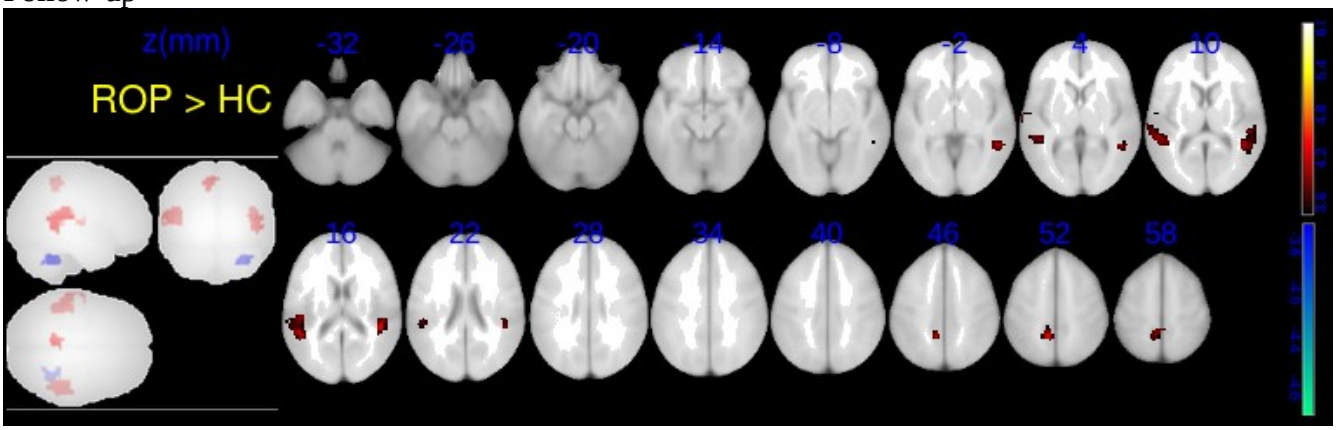
Muschelli J, Nebel MB, Caffo BS, Barber AD, Pekar JJ, Mostofsky SH (2014) Reduction of motion-related artifacts in resting state fMRI using aCompCor. *NeuroImage* 96, 22–35.

S5 Cross-sectional analysis of between-group differences, using only those subjects entered in the longitudinal analysis (i.e. those subjects with both baseline and follow-up data, n=82, ROP=42, HC=40).

Baseline

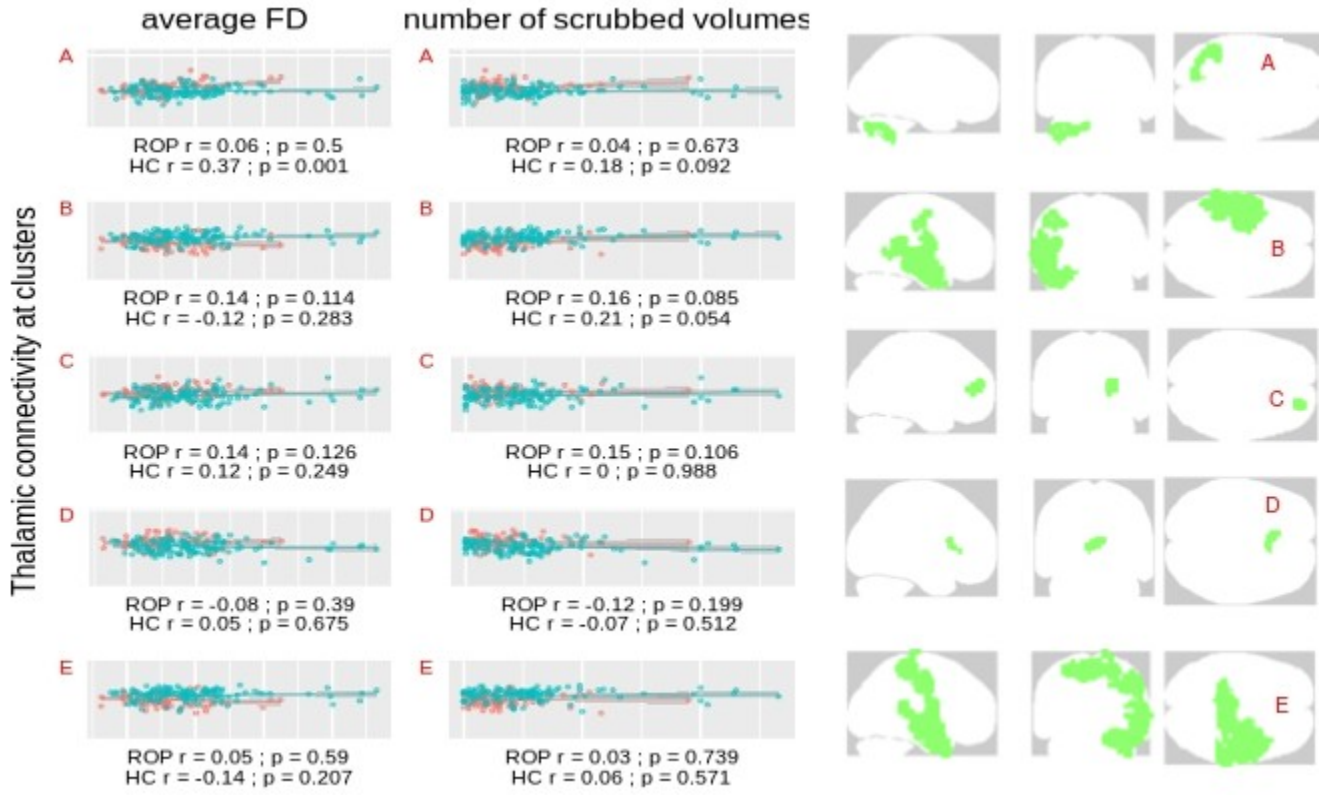


Follow-up



ROP: Recent-onset psychosis; HC: Healthy controls. Between-group significant clusters in thalamic connectivity at baseline from those ROP and controls with available baseline and follow-up data. Red range color scale displays positive correlation with thalamic activity. Red range scale displays higher thalamic connectivity in ROP compared to controls. Blue range scale displays lower connectivity in ROP compared to controls. All results are corrected using an initial cluster-defining threshold of $p<0.005$ at voxel-level and a subsequent cluster-extent FDR correction at $p<0.05$. Note that here the threshold is more tolerant than the threshold used in figure 1 of the main manuscript, to compensate for the reduced sample size.

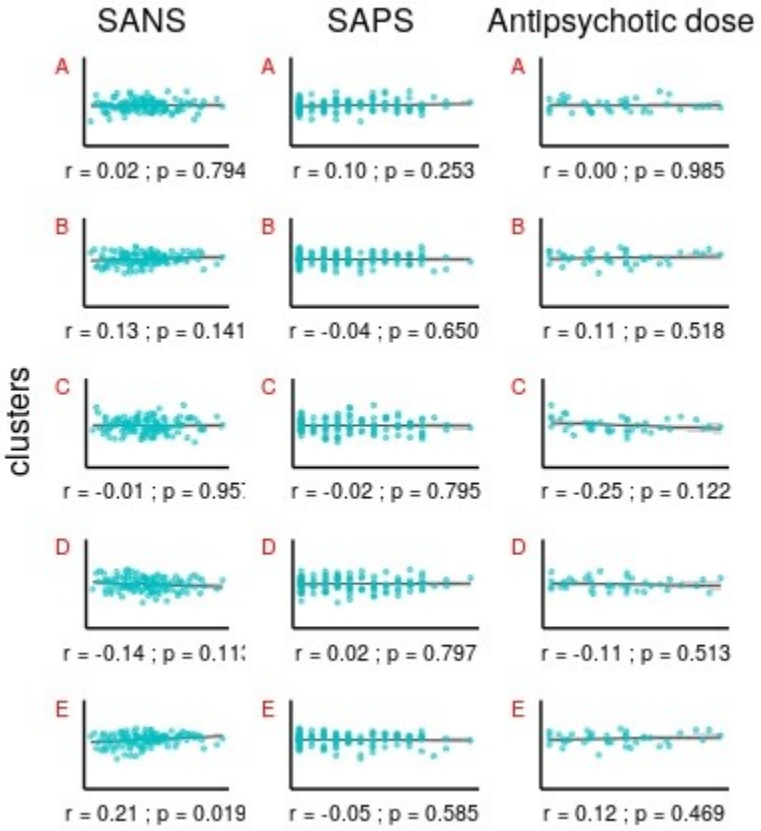
S6: Motion related correlations with connectivity values at main significant clusters in the between-group comparison at baseline.



Significant correlations between thalamic connectivity and motion only occurred in healthy controls in cluster A (left cerebellum). Note that, as previously shown in table S1, on average patients movement was higher than controls, and thus, this spurious correlation is unlikely to account for between group differences in term of thalamic connectivity.

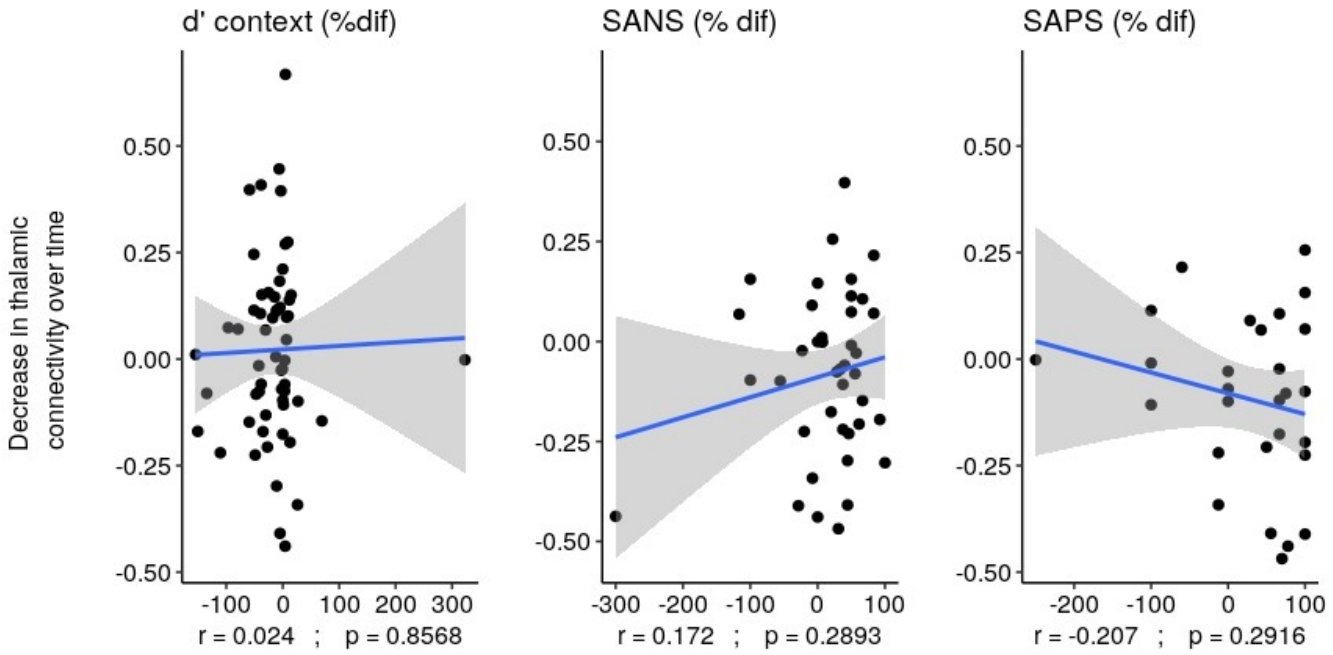
Y-axis in the plots represents thalamic connectivity at the green cluster on the right of the figure. X-axis represent average Frame-wise displacement (FD) per subject (left plots) and total number of scrubbed volumes per subject (right plots). Red dots represent healthy controls and blue dots represent recent-onset psychosis subjects. ROP: Recent onset psychosis, HC: Healthy controls, r: Pearson correlation coefficients, *p:* significance level. Black line represents the regression line within the whole sample.

S7: Clinical correlations with connectivity values at main significant clusters in the between-group comparison at baseline.



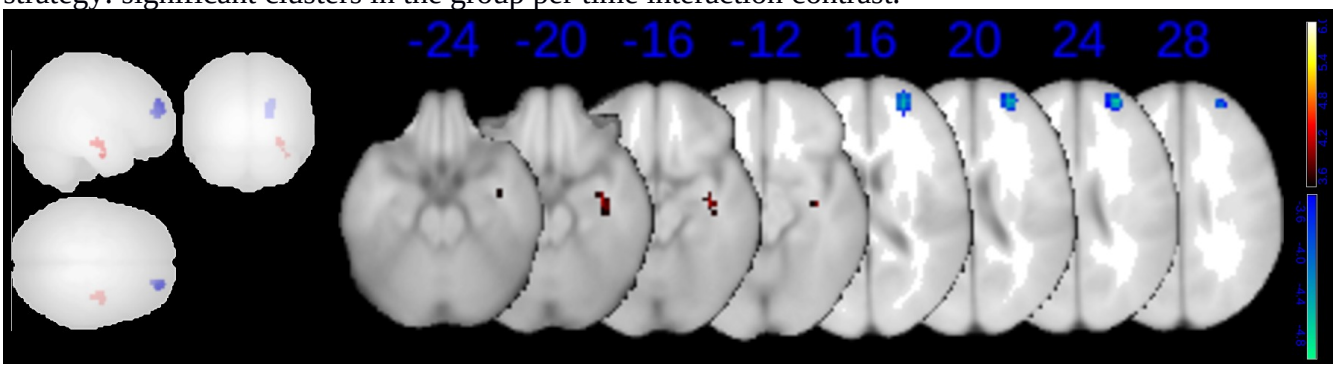
Y-axis in the plots represents thalamic connectivity at each cluster (see green clusters in fig S3 above). X-axis represents scores of the Scale for the Assessment of Negative Symptoms (SANS) for plots in the first column, Scale for the Assessment of Positive Symptoms (SAPS) for plots on the second column, and average antipsychotic dose in chlorpromazine equivalents at scanning time for plots on the last column. Red dots represent healthy controls and blue dots represent recent-onset psychosis subjects. r: Pearson correlation coefficients, *p:* significance level. Black line represents the regression line within the whole sample.

S8. Plots and correlations between decrease in symptoms over time and decrease in thalamic connectivity over time extracted from the only significant cluster of the group*time interaction in the group of recent-onset psychosis.



Y-axis in the plots represents thalamic connectivity at the only significant cluster of the group*time interaction (see figure 2 and table 3 in the main manuscript). X-axis represents percent change (% dif) of d' context in the AX-CPT task (left plot), score percent change of the Scale for the Assessment of Negative Symptoms (SANS), and score percent change of the Scale for the Assessment of Positive Symptoms (SAPS). r: Pearson correlation coefficients, *p:* significance level. Blue line represents the regression line.

S9: Secondary analysis using global signal regression (GSR) instead of the default aCompCor strategy: significant clusters in the group per time interaction contrast.



Red range scale displays decrease over time of thalamic connectivity in recent-onset psychosis (ROP) compared to controls. Blue range scale displays increase over time of thalamic connectivity in ROP compared to controls. All results are corrected using an initial cluster-defining threshold of $p<0.001$ at voxel-level and a subsequent cluster-extent FDR correction at $p<0.05$.