Mapping Thalamocortical Functional Connectivity in Chronic and Early Stages of Psychotic Disorders

Supplemental Information

SUPPLEMENTAL METHODS AND MATERIALS

Study Procedures

Patients were recruited through the Psychotic Disorders Program at the Vanderbilt Psychiatric Hospital. Healthy individuals were recruited from Nashville and surrounding area via advertisement and word-of-mouth. All study participants provided written informed consent prior to participating. Study participants (*n* = 139; 77 healthy subjects, 62 individuals with psychosis-almost all chronic patients) were included in our prior study (1). Psychiatric diagnoses were confirmed in patients and ruled out in healthy subjects using the Structured Clinical Interview for DSM-IV Disorders (SCID: 2). Patients were further assessed with the Positive and Negative Syndrome Scale (PANSS: 3) to quantify severity of clinical symptoms. The Wechsler Test of Adult Reading (4) was administered to all subjects to provide an estimate of pre-morbid intellect. Study participants also completed the Screen for Cognitive Impairment in Psychiatry (SCIP: 5), a brief neuropsychological battery that includes a word list learning test of verbal memory, a version of the Auditory Consonant Trigrams test of working memory, phonemic verbal fluency, and a coding test of processing speed. SCIP sub-test raw scores were converted to z-scores using previously published normative data and averaged to create a “global” z-score of overall cognitive functioning (5). Exclusion criteria included age less than 16 or greater than 65; estimated pre-morbid IQ less than 70; presence of a medical illness or central nervous system disorder (e.g., multiple sclerosis, epilepsy) that would affect study results; reported pregnancy or lactation; history of significant head trauma; psychotropic drug use (healthy subjects only); substance abuse within last one month (patients) or lifetime history of substance abuse/dependence (healthy subjects); first degree relative with a psychotic illness (healthy subjects only); and MRI contra-indicators (e.g. metal implants, claustrophobia).

Imaging Data Acquisition and Pre-Processing

Imaging data were collected on two identical 3T Philips Intera Achieva MRI scanners located at Vanderbilt University Institute of Imaging Science. A 7-minute echo-planar imaging resting-state scan with the following parameters was collected on each individual: 28 axial slices, matrix = 80 × 80, 3.0 mm × 3.0 mm in-plane resolution, slice thickness = 4.0 mm, 203 volumes, TR/TE = 2000/35 ms. Subjects were instructed to rest quietly with their eyes closed and to remain awake during the scan. A high resolution T1-weighted fast field echo (FFE) structural scan (170 sagittal slices, matrix = 256 × 256, 1.0 mm isovoxel resolution, TR/TE = 8.0/3.7 ms) was also acquired on every individual. The resting-state scan was acquired immediately after the survey and high resolution structural scan, and was not preceded by a cognitive task. Imaging data preprocessing, performed within SPM8 (http://www.fil.ion.ucl.ac.uk/spm), included head motion correction, correction for slice-timing offset, and spatial coregistration to anatomical images. Anatomical images were segmented into gray, white and CSF using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm). Each subject's native space gray matter segmentation was normalized to the a-priori gray matter MNI template included in SPM8. The coregistered native space functional data were then normalized to MNI using the normalization parameters derived from the anatomical normalization procedure. Consistent with prior thalamocortical resting-state studies, no spatial smoothing was applied to the functional data (1,6,7).

SUPPLEMENTAL RESULTS

Cortical ROI-to-Thalamic ROI Analysis: Supplemental Analyses Controlling for Scanner, Head Motion, and Age and Sex Effects

Healthy subjects and patient groups (i.e., early stage, chronic) differed on head motion, scanner assignment, age, and sex. To confirm that the results of the primary analysis reported in the text were not confounded by group differences in these variables, we performed a series of supplemental analyses controlling scanner, head motion, age, and sex.

First, we performed additional repeated measures ANOVAs adding head motion and scanner as additional covariates. As shown in Figure S2, adding these covariates had little effect on the main findings. After adjusting for number of "scrubbed" volumes, the group x network interaction remained significant ($F_{(10,488)}$ = 3.27, p = .0004) as did the univariate ANOVAs examining group differences in PFC-thalamic ($F_{(2,247)}$ = 5.78, p = .004), motor-thalamic ($F_{(2,247)}$ = 9.00, p < .001), and somatosensory-thalamic ($F_{(2,247)}$ = 4.86, p = .008) networks. In each case, the original post-hoc findings remained significant; PFC-thalamic connectivity was reduced in early stage (p = .021) and chronic (p = .002) patients, whereas motor-thalamic and somatosensory-thalamic connectivity was increased in both patient groups compared to healthy subjects (motor-thalamic: early stage (p = .024), chronic (p < .001); somatosensory-thalamic: early-stage (p = .019), chronic (p = .009)). After adjusting for scanner, the group x network interaction remained significant ($F_{(10,488)}$ = 2.70, p = .003) as did the univariate ANOVAs examining group differences in PFC-thalamic ($F_{(2,247)}$ = 4.22, p = .016), motor-thalamic ($F_{(2,247)}$ = 7.46, p = .001), and somatosensory-thalamic ($F_{(2,247)}$ = 4.18, p = .016) networks. In each case, the original post-hoc findings remained significant; PFC-thalamic connectivity was reduced in early stage (p = .035) and chronic (p = .012) patients, whereas motor-thalamic and somatosensory-thalamic connectivity was increased in both patient groups compared to healthy subjects (motor-thalamic: early stage (p = .036), chronic (p < .001); somatosensory-thalamic: early-stage (p = .018), chronic (p = .015)).

Second, we performed several case-control analyses in which as many patients as possible within the early stage and chronic group were paired to a healthy subject matched for age, sex, or head motion. To avoid potential bias introduced by post-hoc sorting, we used the "Case Control Matching" algorithm in the IBM Statistical Package for the Social Science (SPSS) to identify case-control pairs. Because the total number of patients was substantially larger than the number of healthy subjects (n = 148 vs. n = 105), matching was done separately for early stage and chronic groups in order to maximize the number of potential matches. To avoid

violations of independence, case-control comparisons were done separately for each patient group, rather than running an ANOVA with both patient groups and matched controls.

For the early stage patients, 46 case-control pairs matched on sex and age (within ± 3 years) were identified. As expected, the groups were well matched on age (patients: 22.6 ± 3.7; healthy subjects: 23.0 ± 3.7; $t_{(90)}$ = 0.54, p = .589). Consistent with the primary ROI-to-ROI analysis, the repeated measures ANOVA with network included as the repeated measure and group the between subjects variable revealed a significant group x network interaction ($F_{(5,86)}$ = 2.88, p = .019). Follow-up independent group *t*-tests revealed significantly greater PFC-thalamic connectivity in healthy subjects ($t_{(90)}$ = 1.98, p = .058), and significantly greater motor-thalamic and somatosensory-thalamic connectivity in early stage patients ($t_{(90)}$ = 1.94, p = .055; and $t_{(90)}$ = 2.33, p = .022, respectively).

For the chronic patients, 74 case-control pairs matched on sex and age (within ± 3 years) were identified. As expected, the groups were well-matched on age (patients: 36.0 ± 11.2; healthy subjects: 35.7 ± 11.3; $t_{(146)}$ = 0.18, p = .855). Consistent with the primary ROI-to-ROI analysis, the repeated measures ANOVA with network included as the repeated measure and group the between subjects variable revealed a significant group x network interaction ($F_{(5,142)}$ = 4.27, p = .001). Follow-up independent group t-tests revealed significantly greater PFC-thalamic connectivity in healthy subjects ($t_{(146)}$ = 2.89, p = .005), and significantly greater motor-thalamic and somatosensory-thalamic connectivity in chronic patients ($t_{(146)}$ = 4.43, p < .001; and $t_{(146)}$ = 2.54, p = .012, respectively).

With respect to head motion, given the above findings showing virtually identical results in early stage and chronic patients, we combined early stage and chronic patients into a single patient group and identified 97 case-control pairs matched on sex, age (within ± 3 years) and post-motion scrubbing root mean square framewise displacement (rmsFD within ± 0.1). As expected, healthy subjects were virtually identical in age (healthy subjects: 31.9 ± 11.4; patients: 32.0 ± 11.7; $t_{(192)}$ = 0.06, p = .951) and post-motion scrubbing rmsFD (healthy subjects: 0.18 ± 0.059; patients: 0.18 ± 0.065; $t_{(192)}$ = 0.06, p = .951). Consistent with the primary analysis, the repeated measures ANOVA with network included as the repeated measure and group the between subjects variable revealed a significant group x network interaction ($F_{(5,188)}$ = 3.57, p = .004). Follow-up independent group *t*-tests revealed significantly greater PFC-thalamic connectivity in healthy subjects ($t_{(192)}$ = 2.35, p = .020), and significantly greater motor-thalamic and somatosensory-thalamic connectivity in patients ($t_{(192)}$ = 3.35, p = .001; and $t_{(192)}$ = 2.38, p = .018, respectively).

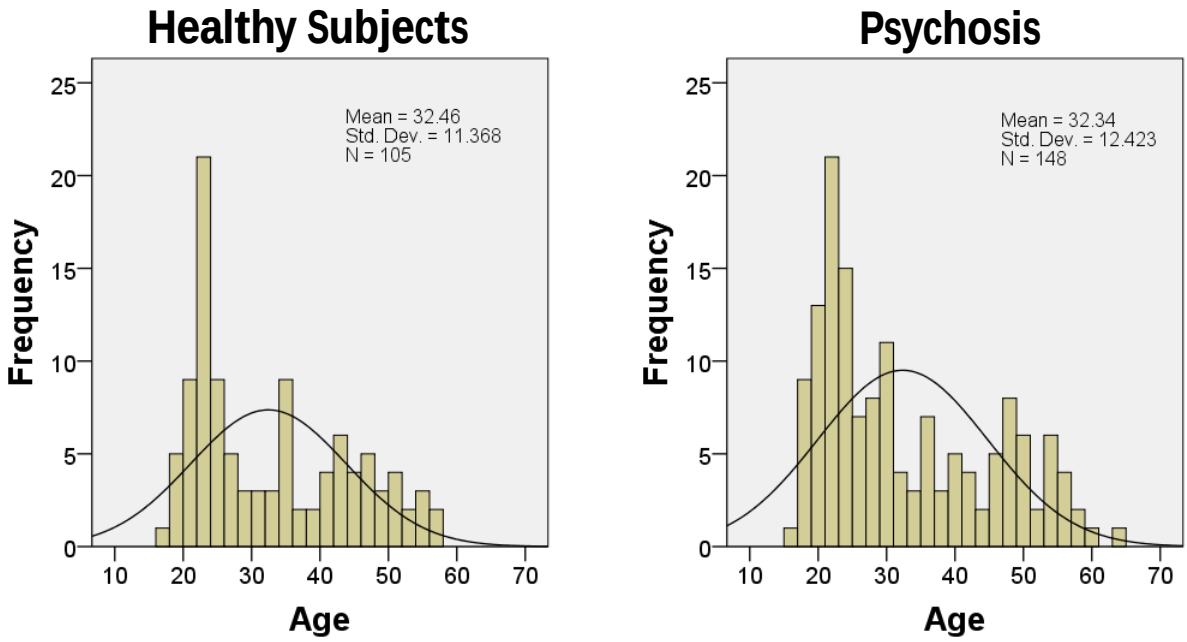

Figure S1. Distribution of ages in the healthy subject and psychotic disorders groups.

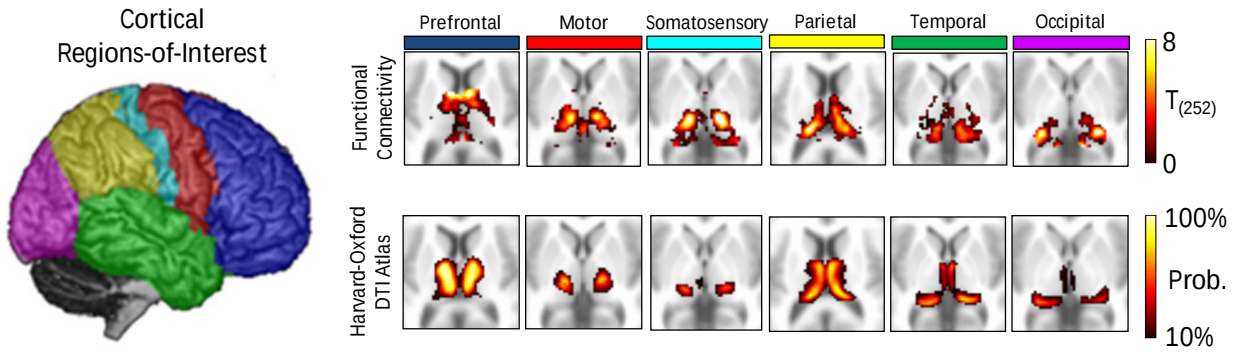

Figure S2. Correspondence between thalamocortical functional connectivity (*n* = 253) and the Harvard-Oxford thalamus probabilistic tractography atlas. In general, there was good agreement between functional connectivity and the Harvard-Oxford probabilistic atlas. However, prefrontal functional connectivity appeared less extensive compared to the Harvard-Oxford atlas. This may be due to the fact that over half the subjects in our entire cohort (*n* = 148 out of 253) had a psychotic disorder, which is associated with reduced prefrontal-thalamic connectivity.

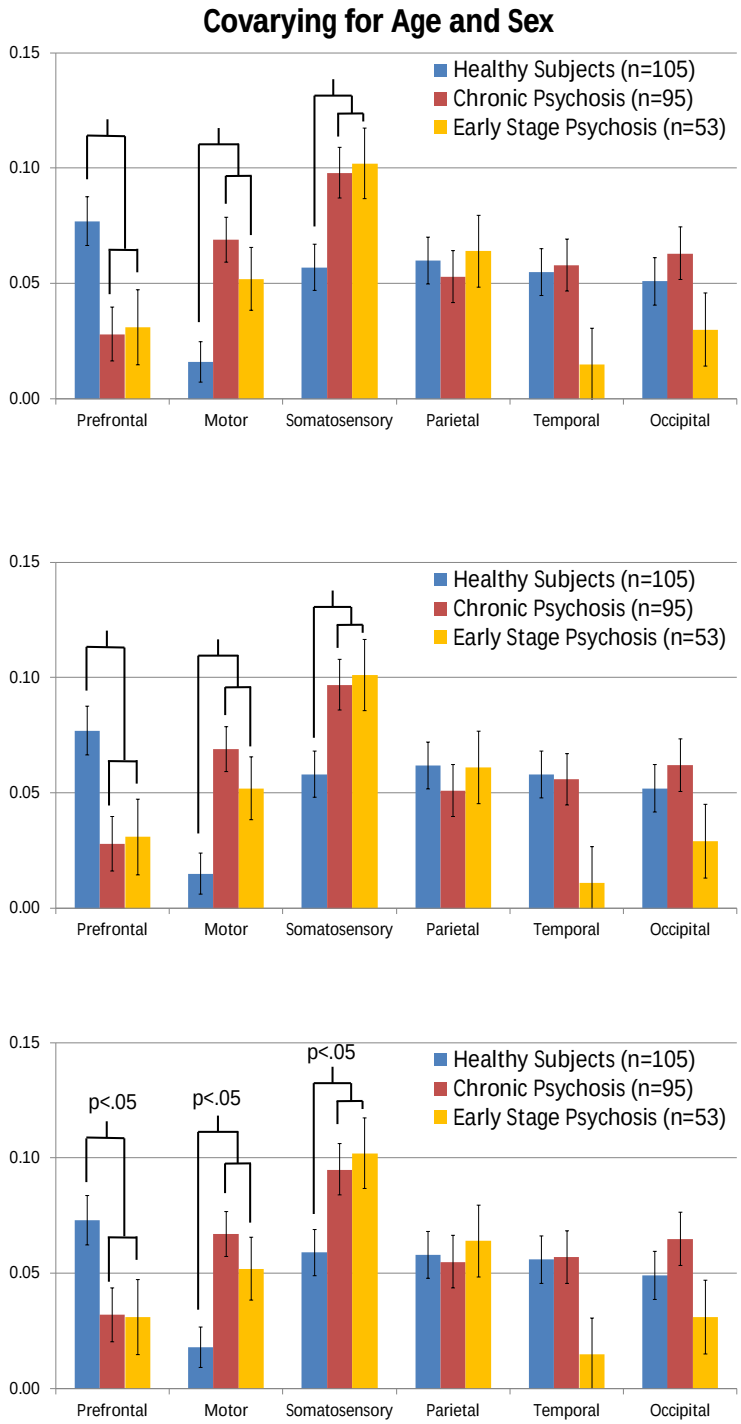

Figure S3. Thalamocortical dysconnectivity in psychosis: motion scrubbing and scanner effects on cortical ROI to thalamic ROI analysis. Top Panel: Group differences after adjusting for age and sex (group x network interaction: $F_{(10,490)} = 3.20$, $p = .001$). Middle Panel: Group differences after adjusting for age, sex, and percentage of "scrubbed" volume (group x network interaction: $F_{(10,488)} = 3.27$, $p = .0004$). Bottom Panel: Group differences after adjusting for age, sex, and scanner (group x network interaction: $F_{(10,488)} = 2.70$, $p = .003$). Errors bars indicate standard error of the mean.

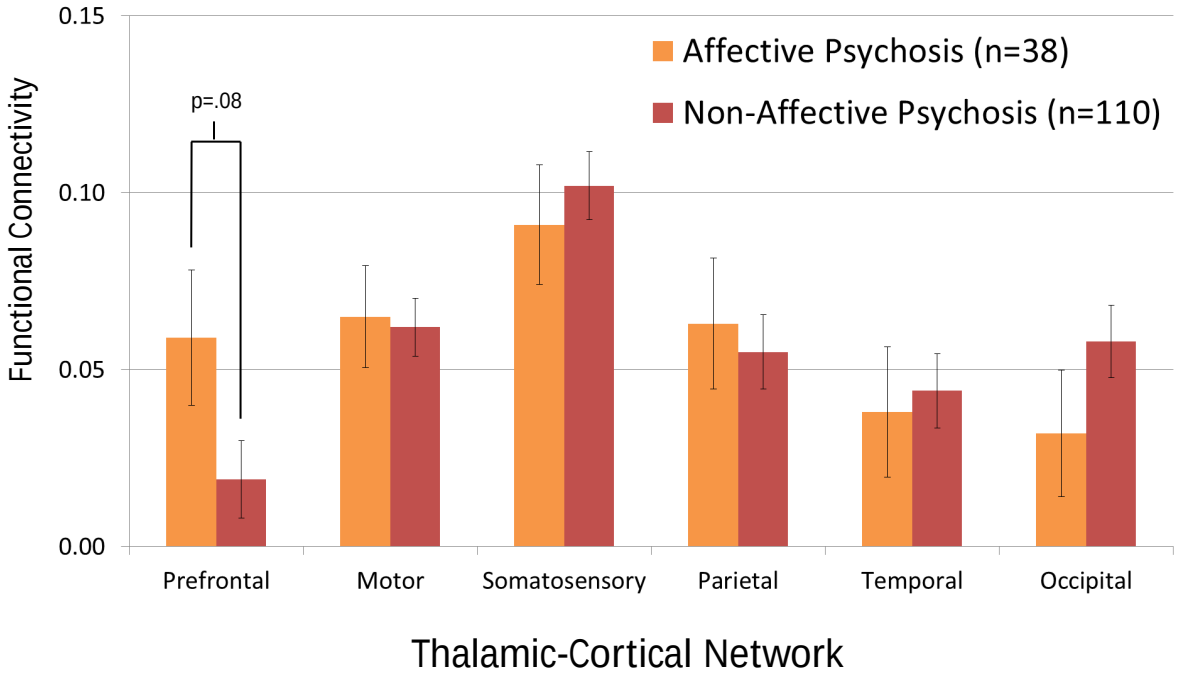

Figure S4. Thalamocortical network connectivity in non-affective and affective psychosis: Cortical ROI to thalamic ROI analysis. After adjusting for age, sex, and illness stage (i.e., chronic, early stage), PFC-thalamic network connectivity was lower in non-affective psychosis compared to affective psychosis ($F_{(1,143)} = 3.11$, $p = .080$). No group differences were detected in the remaining thalamic-cortical networks (all F-values < 1.49, $p > .224$). Error bars indicate standard error of the mean.

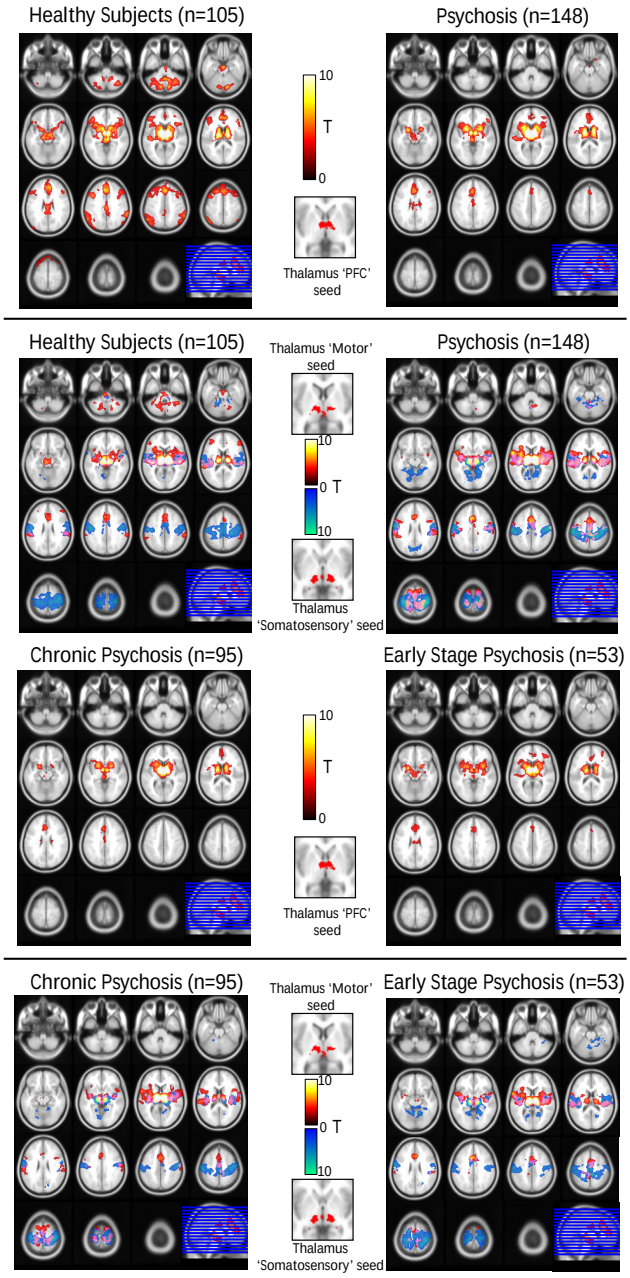

Figure S5. Functional connectivity of thalamus PFC, motor, and somatosensory seeds in healthy subjects and individuals with psychosis, all patients and broken down into chronic and early stage.

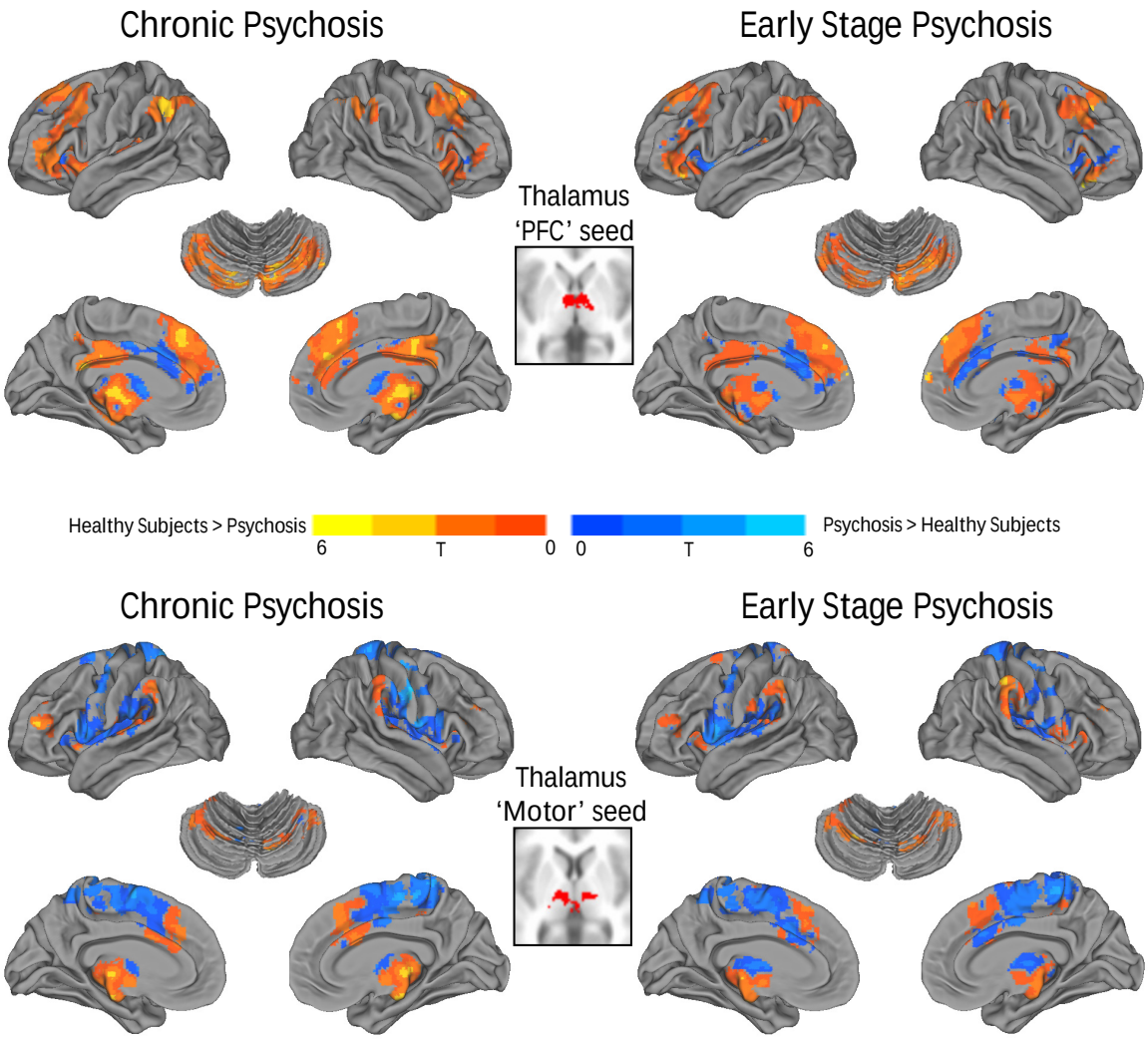

Figure S6. Functional connectivity of the prefrontal and motor thalamic seed regions in chronic and early stage psychosis patients compared to healthy subjects. No statistical threshold was applied to the contrasts in order to show to the similarities in functional dysconnectivity in chronic and early stage psychosis.

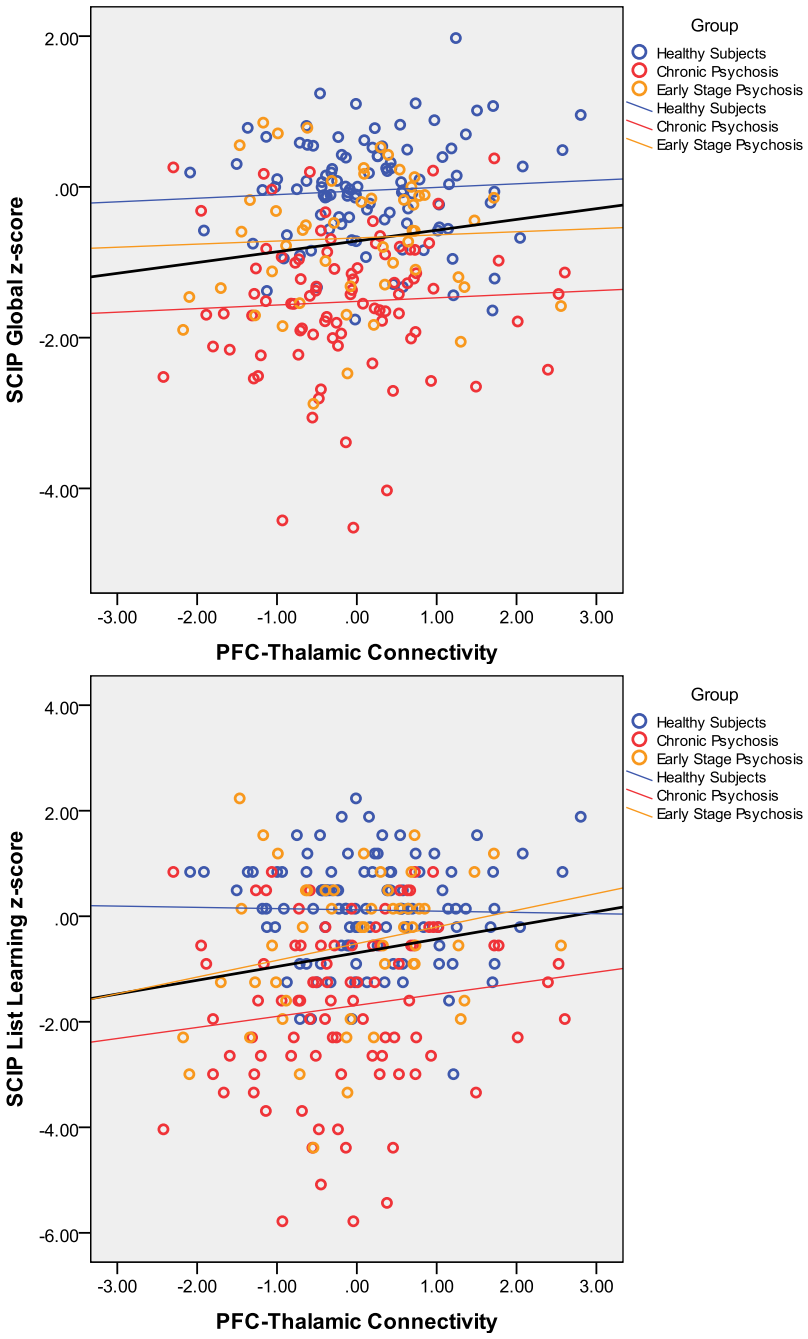

Figure S7. PFC-thalamic functional connectivity and cognitive functioning. Average thalamic functional connectivity was extracted from the PFC clusters identified in the thalamus PFC seed between groups voxel-wise analysis and correlated with cognitive functioning. Across all subjects, average PFC-thalamic functional connectivity correlated with SCIP Global z-score and SCIP List Learning subtest z-score (partial correlation after adjusting for group: r = .14, p = .029 and r = .18, p = .006, respectively). Black lines indicate regression line for the entire cohort of subjects. Regression lines for healthy subjects, chronic patients, and early stage patients are shown in blue, red, and orange, respectively. PFC-thalamic functional connectivity is in residual z-score units after removing group effect.

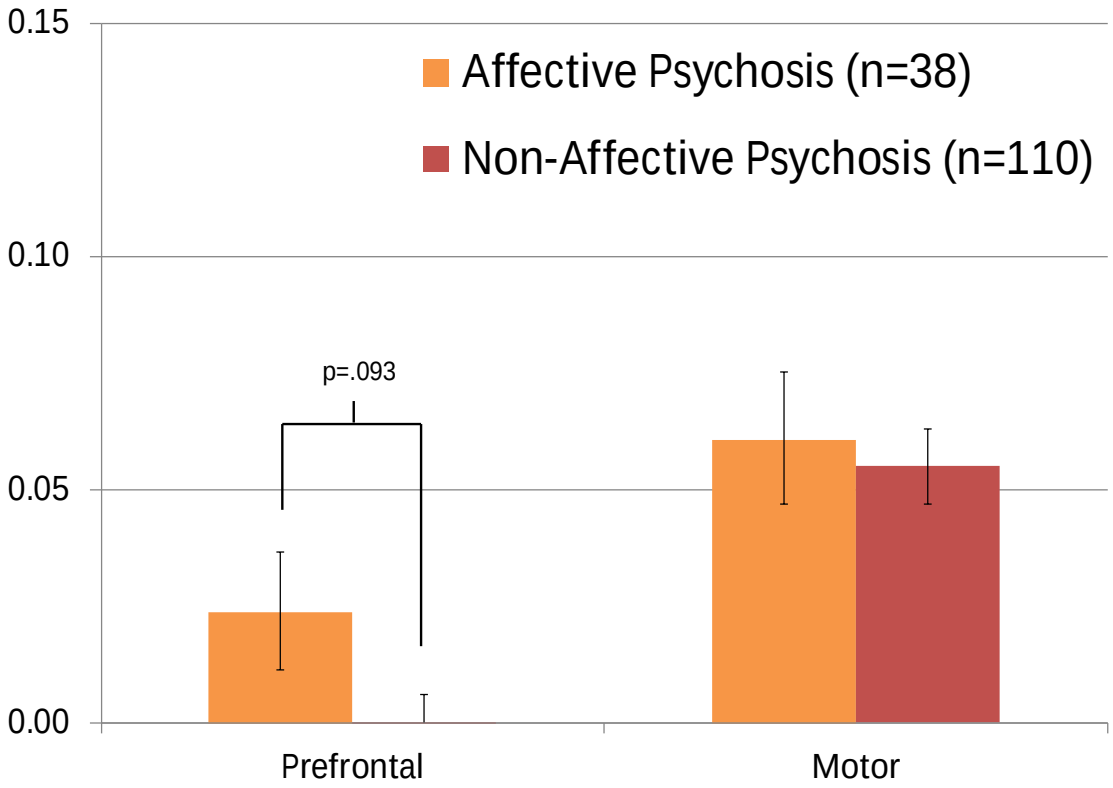

Figure S8. Thalamus seed functional connectivity with regions demonstrating altered functional connectivity in psychosis. Functional connectivity, in beta units, was extracted from the clusters demonstrating altered functional connectivity with prefrontal and motor thalamic seeds in psychosis patients and averaged to create one value indicating average PFC thalamic seed hypo-connectivity and another indicating the average motor thalamus seed hyper-connectivity. After adjusting for age, sex, and illness stage (i.e., chronic, early stage), PFC thalamus seed hypo-connectivity was more severe in non-affective psychosis compared to affective psychosis at the trend significance level ($F_{(1,143)}$ = 2.86, p = .093). Average motor thalamus seed hyper-connectivity did not differ between groups ($F_{(1,143)}$ = 0.12, p = .730). Error bars indicate standard error of the mean.

SUPPLEMENTAL REFERENCES

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