Enhanced functional connectivity between sub-regions in the thalamus and cortex in schizophrenia patients measured by resting state BOLD fMRI at 7T

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PURPOSE: The thalamus is an important deep grey matter structure that relays information between subcortical and cortical regions. Altered thalamocortical connectivity has been reported in schizophrenia (SCZ) (1,2). However, previous functional connectivity studies in SCZ used the entire thalamus as a single node. The thalamus can be subdivided into multiple distinct nuclei with different anatomical connections to various cortical regions (3,4). It is therefore important to investigate functional connectivity between sub-regions in the thalamus and the cortex in SCZ. One main challenge for such studies is the need of high spatial resolution and sensitivity for fMRI, as the thalamus is a relatively small structure. Here, ultra-high field (7T) BOLD fMRI was employed, which has shown a supra-linear boost of BOLD sensitivity with field strength (5). The Oxford thalamic connectivity atlas (3,4) was adopted to define sub-regions in the thalamus. Functional connectivity between these sub-regions and the whole brain was calculated and compared in SCZ patients and controls.

METHODS: 14 SCZ patients and 14 matched controls were recruited for this study. *The Oxford thalamic connectivity atlas* (3,4) was generated using diffusion based structural connectivity in white matter between the thalamus and cortex. The thalamus was segmented into seven sub-regions, with >25% probability of connection to seven exclusive cortical areas, respectively (Table 1). Note that this is a probabilistic atlas thresholded at 25%. Therefore, many voxels within one sub-region can still have connections to cortical regions other than their assigned primary cortical target (4,6). *Experiments* were performed on a 7T Philips scanner. A resting state fMRI scan was performed with GRE EPI (TR/TE/FA=2000/22ms/60º, voxel=2.5mm iso, 54 slices, 7min). *Data analysis* was carried out with SPM8 / Matlab6. Preprocessing includes realignment, slice time correction, co-registration, segmentation, normalization; nuisance removal (CompCor), regression of global mean and motion parameters; spatially smoothing (5mm kernel) and temporal filtering (0.01-0.1Hz). *Seed-based analysis* was carried out using each thalamic sub-region as a seed, and whole brain connectivity maps to each seed were calculated. *T-tests* were performed to examine differential connectivity between SCZ patients and controls (thresholded at a voxel-level of p<.001 and multiple-comparisons corrected at a cluster-level threshold of p<.05). Effect size was estimated with Cohen's *d*.

RESULTS: In controls, all thalamic sub-regions showed significant functional connectivity with their corresponding cortical areas defined in the anatomical connectivity atlas (data not shown). Besides, each thalamic sub-region also had functional connections to multiple cortical areas other than its primary target. Enhanced functional connectivity between thalamic sub-regions and various cortical areas was detected in SCZ (partial list in Table 2, due to space limit), which include both primary targets and other regions (non-primary, shaded in Table 2). The negative and positive correlations between thalamic and cortical regions in controls and SCZ, respectively, are consistent with previous reports using the thalamus as a single seed (1,2). Enhanced connectivity was observed between all thalamic sub-regions and the motor cortex. Enhanced connectivity to the temporal cortex was detected in several thalamic sub-regions, except for sub-region 7 that has the highest anatomical connection probability in controls (primary target). Reduced connectivity in SCZ was also found, mainly between some thalamic sub-regions and sub-cortical areas such as the caudate (data not shown).

DISCUSSION: Our results showed altered thalamocortical functional connectivity across multiple brain regions in SCZ. This is consistent with previous studies at 3T and lower fields. In addition, these preliminary 7T findings lead to the hypothesis that many, but not necessarily all, thalamic functional connections are altered in SCZ. Also, the specific involvement of subregions may ultimately lead to a better understanding of the disease. The SCZ patients in this study were all under medication, the effects from which should be further evaluated. To match the SCZ patients, most control subjects recruited for this study are regular smokers. Therefore, the functional connectivity data in controls may be different from normal subjects in other studies. .

CONCLUSION: Enhanced functional connectivity between sub-regions in the thalamus and cortex in SCZ patients was demonstrated using resting state BOLD fMRI at 7T. Our results may improve the understanding of functional brain changes in SCZ, and may serve as potential surrogate markers for clinical trials.

Table 1. Thalamic sub-regions defined by structural connectivity.

Thalamic subregion	Cortical connection
1. VLp	Primary motor
2. LP, VPL	Somatosensory
3. LGN, some Pu and intralaminar nuclei	Occipital
4. MD, VA, AM, AD	Prefrontal
5. VLa, VA	Premotor
6. anterior Pu	Posterior parietal
7. MD, some medial and inf Pu	Temporal lobe

Table 2

Region	Hemis-phere	Size (#voxels)	Connectivity (z values) SCZ mean	Std	Control mean	std	Effect size
Sub-region 1 (connection to primary motor), SCZ>control							
Precentral	R/L*	120	0.096	0.059	-0.046	0.077	2.15
Paracentral_Lobule	L	60	0.082	0.065	-0.047	0.066	2.04
Parietal_Sup†	L	50	0.016	0.063	-0.066	0.056	1.43
Postcentral	R/L	140	0.069	0.054	-0.056	0.075	1.99
Supp_Motor_Area	R/L	71	0.092	0.063	-0.041	0.055	2.33
Temporal_Inf	R	101	0.02	0.062	-0.091	0.038	2.24
Sub-region 2 (connection to sensory), SCZ>control							
Postcentral	R/L	150	0.072	0.054	-0.055	0.069	2.13
SupraMarginal	R/L	23	0.054	0.063	-0.051	0.065	1.70
Frontal_Sup	R/L	50	0.036	0.051	-0.054	0.03	2.23
Precentral	R/L	170	0.1	0.065	-0.047	0.082	2.06
Supp_Motor_Area	R/L	161	0.09	0.058	-0.034	0.07	2.00
Temporal_Mid	L	178	0.014	0.024	-0.074	0.054	2.19
Sub-region 3 (connection to occipital), SCZ>control							
Postcentral	R	153	0.073	0.05	-0.04	0.085	1.68
Precentral	R	128	0.09	0.056	-0.039	0.085	1.86
Temporal_Sup	R	92	0.042	0.041	-0.024	0.096	0.93
Sub-region 4 (connection to prefrontal), SCZ>control							
Frontal_Inf_Oper	L	29	0.037	0.038	-0.051	0.042	2.28
Frontal_Inf_Tri	L	71	0.011	0.037	-0.071	0.04	2.21
Insula	L	104	0.082	0.04	-0.029	0.044	2.74
Postcentral	R/L	196	0.08	0.053	-0.058	0.074	2.23
Precentral	R/L	262	0.102	0.072	-0.051	0.086	2.00
Supp_Motor_Area	R/L	119	0.098	0.061	-0.04	0.068	2.22
Temporal_Sup	L	122	0.048	0.039	-0.073	0.067	2.29
Sub-region 5 (connection to premotor), SCZ>control							
Supp_Motor_Area	R/L	123	0.098	0.068	-0.037	0.063	2.14
Cingulum_Mid	R/L	107	0.117	0.07	-0.034	0.065	2.32
Postcentral	R/L	146	0.082	0.055	-0.062	0.082	2.14
Temporal_Mid	R	128	0.031	0.052	-0.094	0.048	2.59
Sub-region 6 (connection to posterior parietal), SCZ>control							
Cingulum_Mid	R	81	0.121	0.075	-0.047	0.075	2.32
Parietal_Inf	R	13	0.048	0.069	-0.087	0.065	2.09
Precuneus	L	52	0.046	0.05	-0.062	0.036	2.57
SupraMarginal	R	22	0.053	0.047	-0.051	0.045	2.35
Fusiform	L	53	0.052	0.039	-0.051	0.064	2.02
Precentral	R/L	289	0.102	0.072	-0.047	0.086	1.95
Supp_Motor_Area	R	101	0.096	0.06	-0.038	0.061	2.30
Temporal_Inf	R	64	0.026	0.049	-0.09	0.037	2.77
Sub-region 7 (connection to temporal), SCZ>control: none							

* For regions with both R and L, only the statistics for R are shown here.
† The shaded regions are outside the primary target area for each seed.

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References: (1)Cetin, Neuroimage 2014;117. (2)Klingner, Eur Arch Psych Clin Neurosci 2014;111. (3)Behrens, MRM 2003;1077. (4)Behrens, Nat Neurosci 2003;750. (5)Uludag, Neuroimage 2009;150. (6)Johansen-Berg, Cereb Cortex 2005;31.