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Derin J. Cobia
Brigham Young University - Provo

Matthew J. Smith

Ilse Salinas

Charlene Ng

Mohktar Gado

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Authors

Derin J. Cobia, Matthew J. Smith, Ilse Salinas, Charlene Ng, Mohktar Gado, John G. Csernansky, and Lei Wang

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Progressive deterioration of thalamic nuclei relates to cortical network decline in schizophrenia

Derin J. Cobia, PhD[a], **Matthew J. Smith, PhD, MPE, MSW**[a], **Ilse Salinas, BA**[a], **Charlene Ng, MD**[c], **Mohktar Gado, MD**[d], **John G. Csernansky, MD**[a], and **Lei Wang, PhD**[a,b]

[a]Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, 446 E. Ontario, Suite 7-100, Chicago, IL 60611 USA

[b]Department of Radiology, Northwestern University Feinberg School of Medicine, 446 E. Ontario, Suite 7-100, Chicago, IL 60611 USA

[c]Virginia Commonwealth University, Chesterfield Family Practice Center, 2500 Pocoshock Place, Suite 202, Richmond, VA 23235 USA

[d]Department of Radiology, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110 USA

Abstract

Thalamic abnormalities are considered part of the complex pathophysiology of schizophrenia, particularly the involvement of specific thalamic nuclei. The goals of this study were to: introduce a novel atlas-based parcellation scheme for defining various thalamic nuclei; compare their integrity in a schizophrenia sample against healthy individuals at baseline and follow-up time points, as well as rates of change over time; examine relationships between the nuclei and abnormalities in known connected cortical regions; and finally, to determine if schizophrenia-related thalamic nuclei changes relate to cognitive functioning and clinical symptoms. Subjects were from a larger longitudinal 2-year follow-up study, schizophrenia (n=20) and healthy individuals (n=20) were group-matched for age, gender, and recent-alcohol use. We used high-dimensional brain mapping to obtain thalamic morphology, and applied a novel atlas-based method for delineating anterior, mediodorsal, and pulvinar nuclei. Results from cross sectional GLMs revealed group differences in bilateral mediodorsal and anterior nuclei, while longitudinal models revealed significant group-by-time interactions for the mediodorsal and pulvinar nuclei. Cortical correlations were the strongest for the pulvinar in frontal, temporal and parietal regions, followed by the mediodorsal nucleus in frontal regions, but none in the anterior nucleus. Thalamic measures did not correlate with cognitive and clinical scores at any time point or longitudinally. Overall, findings revealed a pattern of persistent progressive abnormalities in thalamic nuclei that relate to advancing cortical decline in schizophrenia, but not with measures of behavior.

Corresponding Author and Reprint Requests: Derin J. Cobia, PhD, Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, 710 N. Lake Shore Dr., Abbott Hall 1316, Chicago, IL 60611 USA, Office: (312) 503-3984, Fax: (312) 503-0527, d-cobia@northwestern.edu.

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Keywords

schizophrenia; thalamus; nuclei; cortex; longitudinal; cognition

INTRODUCTION

1.1

Cortical and thalamic networks are believed to have pivotal roles in the regulation of key cognitive and emotional functions (Arend et al., 2015; Saalmann and Kastner, 2015). Impaired thalamocortical processing is of particular interest in schizophrenia given its role in regulating and integrating various types of information (Byne et al., 2009; Woodward et al., 2012). Both single and meta-analytic investigations of the thalamus have identified abnormalities in gross volumetrics and voxel-based morphometry (VBM) gray matter density (Konick and Friedman, 2001), as well as in surface-based estimates of thalamic shape (Csernansky et al., 2004b; Harms et al., 2007; Smith et al., 2011a). Overall, thalamocortical disruption is viewed as critical to the neural dysfunction observed in schizophrenia (Byne et al., 2009; Guller et al., 2012), and potentially linked to clinical symptomatology and cognitive impairment (Andrews et al., 2006).

Given the thalamus is comprised of discrete nuclei with afferent and efferent projections that form various segregated thalamocortical loops, investigating their individual contribution to the pathological process of schizophrenia could advance localization of psychosis-related circuitry changes. For example, Byne and colleagues (2001; 2002; 2007) revealed prominent abnormalities in mediodorsal, pulvinar and anterior thalamic nuclei in schizophrenia; subdivisions that are associated with higher-order cognitive and emotional functions (Bonelli and Cummings, 2007). Although longitudinal schizophrenia-related neural abnormalities have long been a topic of interest (DeLisi, 2008), to date there are no studies focused on changes that occur within these specific thalamic subdivisions. Progressive volumetric abnormalities of the thalamus proper have been mixed, with some finding longitudinal change (Andreasen et al., 2011), but others not (James et al., 2004; Nesvåg et al., 2012). These results are noted only in larger investigations of overall brain change in schizophrenia, and the relative lack of broad, but also specific, thalamic change prompts further investigation.

Using longitudinal data from group-matched cohorts, we sought to characterize localized shape deformation of thalamic nuclei related to important cognitive and emotional functions in schizophrenia, namely mediodorsal, pulvinar, and anterior regions. Our primary aims were to: 1) quantify surface estimates of the nuclei using a novel atlas-based parcellation scheme; 2) determine whether time-dependent changes occur in these regions; 3) examine their relationships to known connected cortical regions; 4) investigate whether clinical and cognitive dimensions systematically relate to changes in these regions. We hypothesized that the three identified subdivisions would demonstrate progressive deterioration greater than that observed in healthy individuals based on the behavioral phenotype of schizophrenia that suggests perpetual disruption of these components as described above, and would relate to changes in their cortical counterparts within the circuit. Finally, we anticipated that both

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cross-sectional and time dependent abnormalities in these nuclei would correlate with the cognitive and behavioral dysfunction observed in schizophrenia.

METHODS

2.1. Participants

Participant groups (SCZ = 20, CON = 20; Table 1) were described in a previously published study (Cobia et al., 2012), and come from larger cohorts recruited as part of an ongoing longitudinal study in schizophrenia. A diagnosis of schizophrenia was assessed, and a series of cognitive and symptom measures were administered; see online Supplemental Material for more detailed information.

2.2. MRI Acquisition Parameters

Both FLASH and MPRAGE sequences were collected from participants at the same scanning session for both baseline and ~2-year follow-up visits on a Magnetom 1.5-Tesla Siemens (Erlangen, Germany) scanner with a standard head coil. The Turbo-FLASH sequences (TR = 20 ms, TE = 5.4 ms, flip angle = 30°, 180 slices, field of vision = 256 mm, matrix = 256 × 256, time = 13.5 min) acquired at 1 mm^3 isotropic (Venkatesan and Haacke, 1997) were used for the thalamic processing pipeline. While the MPRAGE sequences (TR = 10ms, TE = 4ms, Flip angle = 30°, ACQ = 1, Matrix = 256 X 256, Scanning time = 5.6 minutes, 1 mm × 1 mm × 1.25mm resolution) were used to derive cortical volume estimates.

2.3. Thalamic Zones Surface Mapping and Cortical Volume Estimates

Generation of surface data, validity and reliability of mapping the thalamus proper using Large-Deformation High-Dimensional Brain Mapping (HDBM-LD) was previously established (Csernansky et al., 2004a). An expert neuroanatomist (MG) identified and delineated three primary thalamic nuclei: anterior (ANT), mediodorsal (MD), and pulvinar (PUL) (Figure 1A); the remaining thalamus was also measured as a single region. This new landmarked atlas was then used to outline the zones on a template surface (Figure 1B). The amount of surface displacement (in mm) from a common template was used as a representation of localized volume loss, and averaged across all vertices within each zone. Longitudinal cortical volume (mm^3) data came in part from our previously published study (Cobia et al., 2012) using the longitudinal pipeline from FreeSurfer release 4.5.0 (Dale et al., 1999). See online Supplemental Material for further details on thalamic and cortical imaging methodology.

2.4. Statistical Analyses

The approach for the current study was conducted in two stages: 1) separate cross sectional analytic models at both baseline (TP1) and follow-up (TP2) time points; and 2) longitudinal analytic models. The rationale for this process was to establish links between thalamic shape and variables of interest at static time points, then determine how progressive changes (i.e., slopes of change) related among the variables.

For TP1 and TP2 cross sectional analyses, average raw surface displacement values for each thalamic zone were entered into ANOVA models to test for group differences in shape

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deformation. In the SCZ group, Pearson bivariate correlations were then conducted between thalamic zone scores and known connected cortical regions based on previous anatomy studies (Bonelli and Cummings, 2007; Jones, 2007; Pergola et al., 2015). These models included:

- ANT nucleus with the rostral anterior cingulate gyrus (RAC)
- MD nucleus with the superior frontal (SFG) and middle frontal (MFG) gyri
- PUL nucleus with the SFG, MFG, superior temporal (STG), middle temporal (MTG) gyri, and superior parietal lobule (SPL)

Because thalamocortical pathways are generally confined to a single hemisphere (Pergola et al., 2015), the models were performed on a per hemisphere basis. Finally, we examined the relationship between thalamic zone scores with neuropsychological and clinical scores in the SCZ group using Pearson correlations.

Longitudinal analysis involved entering raw baseline and follow-up surface displacement values from the ANT, MD and PUL into repeated-measures ANOVA models that tested the main effects of group (between subject factor), hemisphere, and time (within subject factors), and then group-by-time and group-by-hemisphere interactions. Change scores for thalamic subdivisions (using raw average displacement values) were calculated as: *follow-up − baseline = change score*. Cortical volume (in mm^3) change scores were calculated to account for variation in brain size as follows: (*follow-up − baseline)/baseline = change score*. These thalamic change scores were then compared with Pearson models in SCZ alone against the same cortical, cognitive and clinical variables as defined above, as well as against interval medication use and duration of illness (DOI) to determine their influence on progressive change. False Discovery Rate (Benjamini et al., 2001) was used to control for multiple comparisons for all analyses.

RESULTS

3.1. Thalamic Zone Mapping

Thalamic zones (as described above) were mapped on a template surface in atlas space, creating a reference atlas for key nuclei (Figure 2). Validation comparison of surface area from each defined thalamic zone between hand-drawn and automated measures revealed a high degree of reliability. ICC values ranged from 0.901 (MD) to 0.990 (Remainder). See Table 2 and online Supplementary Material for more information.

3.2. Group Differences in Thalamic Zones and Correlations at TP1

ANOVA models examining baseline surface deformation values of thalamic zones between SCZ and CON revealed significant group differences in both left ($F_{1,38}$=10.12, p=0.003) and right ($F_{1,38}$=10.31, p=0.003) MD. In addition, there was a significant group difference in the left ANT ($F_{1,38}$=4.93, p=0.033). There were no differences for the right ANT or bilateral PUL.

Pearson correlations between baseline measurements of thalamic zone deformation and cortical volumes in the *left hemisphere* for SCZ (Table 3) revealed positive relationships

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between: MD with SFG; PUL with SFG, MFG, STG, MTG, and SPL (all $p<0.05$, corrected). None were observed between the ANT and RAC, or MD and MFG. In the *right hemisphere*, positive correlations were noted between: MD with SFG and MFG; PUL with SFG, MFG, STG, MTG, and SPL (all $p<0.05$, corrected). None were observed between the ANT and RAC. Duration of illness, antipsychotic medication use and nicotine consumption were not related to thalamic measures in any systematic way, thus were not utilized in ANOVA or correlation models. No correlations were observed between thalamic nuclei and VWM, SWM, EF, POS, NEG, and DIS domains at baseline.

3.3. Group Differences in Thalamic Zones and Correlations at TP2

ANOVA models examining thalamic surface deformation at follow-up between SCZ and CON revealed significant group differences in both left ($F_{1,38}=12.47$, $p=0.001$) and right ($F_{1,38}=14.96$, $p<0.001$) MD. There was also a significant group difference in the left ANT ($F_{1,38}=5.93$, $p=0.020$). There were no differences for the right ANT, but trend findings in the bilateral PUL (left: $F_{1,38}=3.68$, $p=0.062$; right: $F_{1,38}=3.37$, $p=0.074$).

Pearson correlations between follow-up thalamic zone deformation and cortical volumes (Table 3) in the *left hemisphere* for SCZ revealed positive relationships between: PUL with SFG, MFG, STG, MTG, and SPL (all $p<0.05$, corrected). None were observed between the ANT and RAC, or MD and SFG/MFG. In the *right hemisphere*, positive correlations were noted between: MD with SFG and MFG; PUL with SFG, MFG, STG, MTG, and SPL (all $p<0.05$, corrected). None were observed between the ANT and RAC. No correlations were observed between thalamic nuclei and WM, EM, EF, POS, NEG, and DIS domains at baseline or follow-up.

3.4. Longitudinal Change in Thalamic Zones and Change Score Correlations

Mean and standard deviation values with percent change for each zone are presented in Table 4. Findings from RM-ANOVA models revealed significant effects for group in the MD, and for time in ANT, MD and PUL. Significant group-by-time interactions that survived FDR correction were noted for the MD and PUL (see Table 4). The effect of hemisphere was significant only for the ANT (R>L: $F_{1,38}=13.98$, $p<0.001$).

Pearson models between thalamic and cortical changes scores (Table 3) in the *left hemisphere* for SCZ revealed positive correlations between: PUL with SFG, MFG, STG and SPL. For the *right hemisphere*, positive correlations were observed between: MD with the SFG; PUL with SFG, MFG, STG, and SPL (all $p<0.05$, corrected). Correlations between thalamic change scores and cognitive/clinical change scores yielded no significant findings.

DISCUSSION

4.1

The longitudinal progression of thalamic nuclei implicated in cognitive and behavioral processes has not been specifically studied in schizophrenia to date. To address this gap we applied an atlas-based parcellation scheme of individual nuclei to high-dimensional surface mapping that captured sub-millimeter changes in their shape characteristics. In group-

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matched samples with data that spanned ~2 years, we discovered that schizophrenia subjects experienced greater regional volume loss, characterized by localized surface deformation, in bilateral MD and left ANT nuclei at baseline and follow-up relative to healthy individuals. Additionally, they demonstrated progressive decline in the MD and PUL over time compared to the healthy group. Furthermore, we observed that schizophrenia-related abnormalities in the MD and PUL correlated with frontal, temporal and parietal regions in schizophrenia subjects across time points and over time. We did not observe relationships between thalamic nuclei measures with cognition and clinical symptomatology for any analysis.

To date, investigations of specific thalamic nuclei are sparse but continue to grow (Byne et al., 2009). Most of these studies use either postmortem or MRI methods driven by laborious manually traced segmentations. We present a novel methodology that extends our previous work in quantifying important shape characteristics of deep-brain structures (Csernansky et al., 2004a; Wang et al., 2008) that represents an advancement in localizing key thalamic nuclei related to the complex pathophysiology of schizophrenia. Our automated atlas-based approach informed by an expert neuroanatomist demonstrated strong reliability against hand-drawn procedures, suggesting it is a robust method for quantifying these nuclei. Overall, systematic and reliable measures sensitive to subtle changes in discrete regions will be crucial to proper investigation of this anatomy, particularly if large federated datasets are to be leveraged.

Our findings in the MD are consistent with prior reports using manual tracing (Byne et al., 2001; Hazlett et al., 1999; Shimizu et al., 2008), voxel-based methods (see Bora et al., 2011 for a meta-analysis), or other morphometric procedures (Kang et al., 2008) including efforts from our own group (Harms et al., 2007; Smith et al., 2011b). We also found differences in the left ANT, which is a less studied region in psychosis, but has some limited evidence for gray matter loss (Ananth et al., 2002; Byne et al., 2006). Regarding the PUL, we only found trend differences between groups at the follow-up visit, but did observe significant interaction effects over time in the longitudinal analysis. Structural PUL abnormalities are regularly found in both imaging (Brickman et al., 2004; Byne et al., 2001) and postmortem reports (Byne et al., 2009). Thus, our lack of a strong cross-sectional finding may be related to the chosen metric (shape vs volume), boundary definition differences, or timing of the illness.

Comparison of single time point versus time dependent analyses in our study revealed progressive changes in the MD and PUL, while volume loss in the ANT remained relatively stable. Longitudinal imaging studies of the thalamus in schizophrenia are generally contained within overall brain investigations, and typically not the focus of directed search (Andreasen et al., 2011; Nesvåg et al., 2012; Olabi et al., 2011). Our group previously examined progressive thalamic changes and discovered that over a 2-year period there was little evidence of global thalamic volume change between groups, but found that mean shape deformation yielded significant differences across time, suggesting surface characteristics are sensitive to the subtle changes frequently observed in schizophrenia. (Wang et al., 2008). To our knowledge a dedicated longitudinal analysis of specific thalamic nuclei in psychosis does not exist. Thus, findings from the current study are quite unique in that we observed

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selective nuclei experience deterioration over the course of the illness, particularly those implicated in higher-order complex functions (Arend et al., 2015; Bonelli and Cummings, 2007). Our results also suggest that different mechanisms related to the timing of progressive change may be a critical feature of schizophrenia. For example, a staging theory could be hypothesized where early abnormalities develop in an anterior to posterior fashion along the long axis of the thalamus. Changes initiate in ANT and then stabilize while MD deficits begin and continue to decline as the process courses in a posterior trajectory towards the PUL. While these findings suggest a neurodegenerative model of schizophrenia, they are not entirely outside conceptualizations of a neurodevelopmental pathogenesis (Weinberger, 1987). As noted by Rapoport and colleagues (Rapoport et al., 2005), our theorized model could reflect that 1) it is a continuation of the disease process throughout the lifespan, and 2) it represents an exaggeration of normal brain development, where development does not necessarily imply growth but abnormal change.

Our investigation of relationships between a priori identified cortical regions and their linked thalamic nuclei revealed a unique pattern of results. Our strongest findings were with the PUL nucleus, which was consistently related to the frontal, temporal and parietal regions bilaterally at both baseline and follow-up. These relationships remained when examining correlations between time-dependent changes of those variables, particularly for the right hemisphere. We also found that frontal lobe connections to the MD were more strongly related in the right hemisphere relative to the left at cross-sectional time points and over time. Finally, abnormalities in the ANT nucleus were not systematically related to the RAC indicating a different pathophysiological process may be involved. Out of all of the nuclei we studied, the PUL has the broadest distribution of connections across association cortex (Sherman and Guillery, 2011), and its observed abnormalities were consistently related to the cortex in schizophrenia.

These thalamocortical relationships imply that disconnection models of schizophrenia are due not only to disruption of a single, but multiple, components in the circuit and follow a progressive longitudinal course. Other investigations have also linked schizophrenia-related circuit-level abnormalities where aberrant connectivity in one or multiple regions contributes to the overall pathological process (Ferrarelli et al., 2012; Kubota et al., 2013). In particular, several lines of evidence in the functional imaging literature align with our findings in that perturbation of in one node results in dysfunction of the entire circuit. For example, Guller and colleagues (2012) found reduced thalamic and superior medial frontal cortex response to transcranial magnetic stimulation, along with weaker functional connectivity between these regions in a sample of schizophrenia subjects. In addition, the work of Anticevic and colleagues (2013) using resting-state functional imaging revealed connectivity disturbance in mediodorsal and pulvinar regions of the thalamus that were linked to corresponding prefrontal cortex connectivity alterations. In light of our current findings, these discoveries suggest both structural and functional abnormalities contribute to the pathophysiology of thalamic disruption in schizophrenia, and directly relate to its connected cortical regions. Whether one proceeds the other or they occur in tandem is unclear; however, evidence suggests they are present even in the early course of the illness (Anticevic et al., 2015; James et al., 2004).

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The complete absence of hypothesized cognitive and clinical relationships with our thalamic measures was somewhat surprising. Given evidence from lesion (see Bonelli and Cummings, 2007 for a review) and animal studies (Browning et al., 2015; Parnaudeau et al., 2013; Poulet et al., 2012), we anticipated that some aspects of thalamic change would be reflected in the behavioral manifestations of the illness. Upon further consideration, this finding may not be entirely unexpected given that establishing clear and consistent relationships between brain measures and behavior has been a perpetual challenge in the schizophrenia literature (Antonova et al., 2004). Several explanations for our results are possible: 1) the observed surface-based abnormalities are too subtle to impact cognition in a meaningful way; 2) cognitive functioning in schizophrenia may have stronger relationships with cortical integrity (Ehrlich et al., 2012), thalamocortical functional dynamics (Ferrarelli et al., 2012) or the white matter integrity of its connections (Jakab et al., 2012) than structural abnormalities of the thalamus; 3) the window at which these relationships is best observed is during early or first-episode stages, which had already occurred in our subjects (James et al., 2004); 4) our measures of cognition and clinical symptoms may not be sensitive enough to track thalamic change; and 5) our small sample size is lacking in power to detect subtle or even modest effects between these measures, thus is not in a good position to evaluate these relationships (Friston, 2012).

With these possibilities in mind, limitations of our work must also be considered. First, the small sample size may have limited generalizability; however, the spectrum of illness duration across our subjects was broad, suggesting some adequacy in sampling of various illness stages. Replication in larger samples is certainly encouraged to enhance statistical power, although our ability to carefully group-match subjects based on age, gender, and recent alcohol use may have compensated for some of this inadequacy. Another limitation is that the window of observation for this longitudinal study was only for a period of approximately 2 years. Introducing additional time points over successively longer intervals will assist in understanding the progression of thalamic changes in later illness stages as other factors, such as fluctuation or changes in medication, utilization of rehabilitative strategies and general aging may take effect. In addition, examining other thalamic networks implicated in the clinical presentation of schizophrenia, such as anterior cingulate and orbitofrontal circuitry, may also yield important insights into the pathophysiological process.

In conclusion, this study is the first to our knowledge of a longitudinal analysis of the progression of abnormalities in specific thalamic nuclei in schizophrenia using a surface-based approach. Our novel atlas-based approach to parcellating the nuclei demonstrated strong reliability with hand drawn estimates indicating it is a robust quantitative method. Findings revealed that certain thalamic nuclei experience continued abnormal change over time, and that this relates to abnormal volumetric change in their connected cortical circuit regions. These findings inform theories of abnormal neurodevelopment (Rapoport et al., 2005), as well as those that implicate schizophrenia as a disorder of ‘dysconnection’ that affects distributed neural networks (Andreasen et al., 1998).

Supplementary Material

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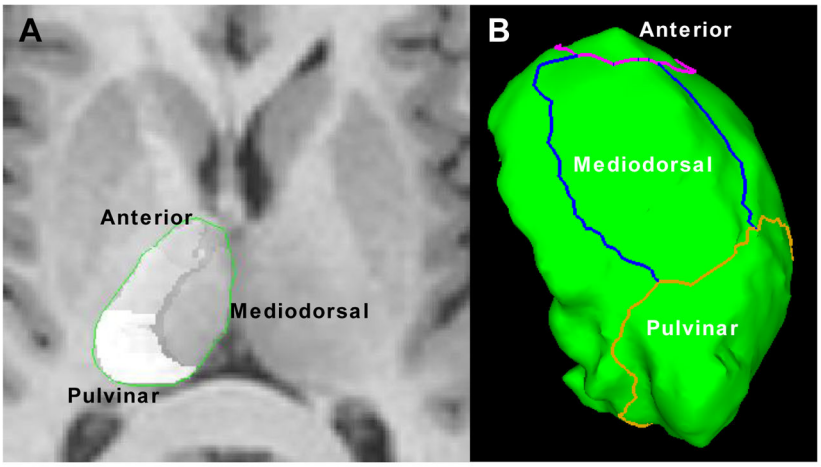

Figure 1.

A) Atlas with thalamic nuclei used to outline four specific zones: Anterior, Mediodorsal, Pulvinar and Remainder on B) a thalamus template

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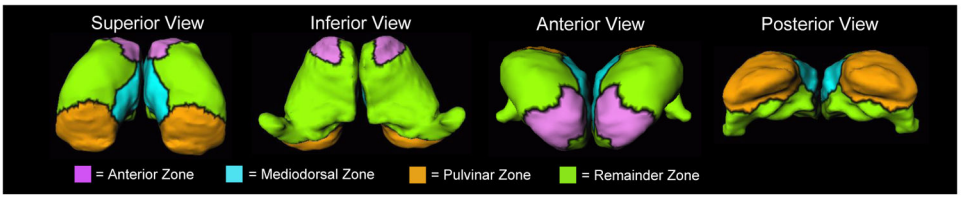

Figure 2.
Surface model of the parcellation scheme for individual thalamic nuclei

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Table 1

Demographic Characteristics of Study Sample

	SCZ (n = 20)		CON (n = 20)		Statistic		
	Mean	**(SD)**	**Mean**	**(SD)**	***t*-test**	**df**	***p***
Age (years)	31.9	(11.1)	30.4	(12.8)	0.41	38	0.68
Parental SES	3.4	(1.1)	2.9	(0.7)	1.97	38	0.06
Alcohol use (grams per year)	2049	(3973)	3235	(5399)	−0.75	34	0.46
Nicotine use (cigarettes per year)	4357	(4088)	611	(1761)	3.77	26	0.001*
Scan Interval (years)	2.0	(0.9)	2.1	(0.4)	−0.41	38	0.68
Duration of Illness (years)	12.4	(12.9)		--			
Chlorpromazine Equivalent (2 years prior to baseline)							
1st-Generation (Dose Years)	1.13	(3.7)		--			
2nd-Generation (Dose Years)	3.47	(3.4)		--			
Chlorpromazine Equivalent (between baseline and follow-up)							
1st-Generation (Dose Years)	0.95	(2.9)		--			
2nd-Generation (Dose Years)	6.64	(5.3)		--			
	N	(%)	N	(%)	X^2	df	*p*
Gender, No. (% male)	10	(50.0%)	11	(55.0%)	0.10	1	0.75
Race (%)					6.93	2	0.03*
Caucasian	8	(40%)	16	(80%)			
African-American	11	(55%)	4	(20%)			
Hispanic	1	(5%)	0	(0%)			
Handedness R/L (%)	18/2	(90/10%)	16/4	(80/20%)	0.78	1	0.38

* $p < 0.05$

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Table 2

Thalamic zone surface area values and comparison

Method	Thalamic Zone Surface Area Values (mm^2)			
	Anterior	**Medial Dorsal**	**Pulvinar**	**Remainder**
Manual Delineation	213.91 ± 18.20	261.05 ± 20.31	542.92 ± 56.89	1414.50 ± 83.77
Automated Delineation	213.43 ± 20.02	254.80 ± 20.98	550.32 ± 63.30	1415.61 ± 81.85
Reliability Estimate (ICC)	0.935	0.901	0.984	0.990

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Table 3

Pearson Correlations (*r*) Between Thalamic Zones and Cortical ROIs

Measure	Time Point/Interval																	
	Baseline						Follow-up						Longitudinal Change					
	SFG	MFG	STG	MTG	SPL	RAC	SFG	MFG	STG	MTG	SPL	RAC	SFG	MFG	STG	MTG	SPL	RAC
Anterior zone																		
Left	-	-	-	-	-	0.38	-	-	-	-	-	0.33	-	-	-	-	-	0.001
Right	-	-	-	-	-	0.39	-	-	-	-	-	0.24	-	-	-	-	-	−0.12
Mediodorsal zone																		
Left	0.49*	0.40	-	-	-	-	0.37	0.26	-	-	-	-	0.26	0.12	-	-	-	-
Right	0.45*	0.60**	-	-	-	-	0.46*	0.66**	-	-	-	-	0.61**	0.43	-	-	-	-
Pulvinar zone																		
Left	0.55**	0.67***	0.61**	0.47*	0.56**	-	0.66**	0.80***	0.64**	0.53**	0.63**	-	0.64**	0.51*	0.67***	0.36	0.63**	-
Right	0.57**	0.66**	0.57**	0.67***	0.58**	-	0.64**	0.79***	0.63**	0.72***	0.66**	-	0.65**	0.56**	0.53*	0.42	0.64**	-

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$ and survive FDR correction for multiple comparisons at a 0.05 level

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Table 4

Mean (SD), Percent Change, and RM-ANOVA Results for Thalamic Zones

Measure	Mean (SD)										Longitudinal Analyses *F* (1, 38) *p*					
	SCZ (*n* = 20)					CON (*n* = 20)					Group Effect		Time Effect		Group-by-Time Interaction	
	Baseline		Follow-up		Change	Baseline		Follow-up		Change						
	Mean	(SD)	(%)	(SD)	(%)	Mean	(SD)	Mean	(SD)	(%)						
Anterior zone											3.69	0.06	**4.83**	**0.03**	2.37	0.14
Left	−0.239	(0.51)	−0.318	(0.57)	−32.79	0.134	(0.56)	0.128	(0.58)	−4.58	--	--	--	--	--	--
Right	−0.040	(0.47)	−0.109	(0.55)	−171.63	0.172	(0.55)	0.152	(0.57)	−11.95	--	--	--	--	--	--
Mediodorsal zone											**13.45**	**0.001**	**9.51**	**0.004**	**7.52**	**0.009**
Left	−0.467	(0.45)	−0.579	(.052)	−24.19	−0.051	(0.37)	−0.061	(0.40)	−19.90	--	--	--	--	--	--
Right	−0.406	(0.43)	−0.515	(0.45)	−26.92	0.026	(0.42)	0.023	(0.43)	−11.36	--	--	--	--	--	--
Pulvinar zone											3.13	0.09	**17.68**	**0.000**	**5.86**	**0.02**
Left	−0.155	(0.41)	−0.250	(0.46)	−61.49	0.034	(0.36)	−0.001	(0.36)	−103.00	--	--	--	--	--	--
Right	−0.170	(0.46)	−0.261	(0.52)	−53.86	0.022	(.040)	0.001	(0.41)	−65.36	--	--	--	--	--	--

Significant ($p < .05$) effects are shown in bold