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

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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.

1. Introduction

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 et al. (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.

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

2. 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 = 10 ms, TE = 4 ms, Flip angle = 30°, ACQ = 1, Matrix = 256 × 256, Scanning time = 5.6 min, 1 mm × 1 mm × 1.25 mm 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) (Fig. 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 (Fig. 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 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

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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