Spherical Registration Distortion and Thalamic Volume in Schizophrenia

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Background and Significance

- Schizophrenia is a devastating illness characterized by skewed perceptions of reality, hallucinations, illusions, delusions and cognitive impairment.
- The neurodevelopmental hypothesis of schizophrenia proposes that maldevelopment of the brain may contribute to the pathophysiology of the illness [1, 2].
  - Studies of cytoarchitecture [3, 4], Gyrification Index [5-7] and abnormal thalamic volume [9, 10] support this hypothesis.
- Based on these studies, we propose that an analysis of surface geometry (namely thickness and folding patterns) and thalamic volume using MRI reconstruction techniques can also reveal patterns of normal brain development [8, 11-14].
  - In the spherical registration of T1-weighted MPRAGE images, the metric distortions reflect the relative differences in surface geometry of the cortex from the population that makes up the atlas.

References:

- [1] Weinberger, DR. Arch Gen Psychiatry 1987;44(7):660-669. [2] Weinberger, DR. Neuropsychopharmacology 1996;14(3S):1-11. [3] Jakob, H, Beckmann H. Neural Transm 1986;65:303-326. [4] Arnold, SE et al. Arch Gen Psychiatry 1991;48:625-632. [5] Kulynych, JJ et al. Biol Psychiatry 1997;41:995-999. [6] Sallet, PC et al. Am J Psychiatry 2003;160:1606-1613. [7] Harris, JM et al. Biol Psychiatry 2004;55:141-147. [8] Narr, KL et al. Am J Psychiatry 2001;158:244-255. [9] Portas, CM et al. Biol Psychiatry 1998;43:649-659. [10] Hazlett, EA et al. Am J Psychiatry 1999;156:1190-1199. [11] Van Essen, DC, Drury, HA. Neuroscience 1997;17(18):7079-7102. [12] Fischl, B et al. NeuroImage 1999;195-207. [13] Fischl, B et al. Human Brain Mapping 1999;8:272-284. [14] Dale, AM et al. NeuroImage 1999;179-194. [15] Richman, DP et al. Science 1975; 189:18-21. [16] Van Essen, DC. Nature 1997;385:313-318.

Reconstruction

- 10 schizophrenic and 8 age-, gender- and handedness-matched control subjects
- T1-weighted MPRAGE images from a Siemens 3T Trio scanner
  - TR 2530, TE 3.45, TI 1100, FA 7, FOV 256, 1.3x1.0x1.3 voxels)
- Brain images were reconstructed and spherically aligned using Freesurfer (fig. 1).
  - http://surfer.nmr.mgh.harvard.edu
- Cortical folding patterns were aligned between subjects using a spherical atlas based on the following energy function (fig. 2):

  $J_c+\lambda_d J_d+\lambda_T J_T$

  J_c: Correlation error (aligns folding patterns)

  J_d: Metric distortion (constrains allowable shape differences)

  J_T: Topology term (forces mapping to be invertible)
- Cortical thickness and metric distortions were measured across the entire brain for both cohorts.

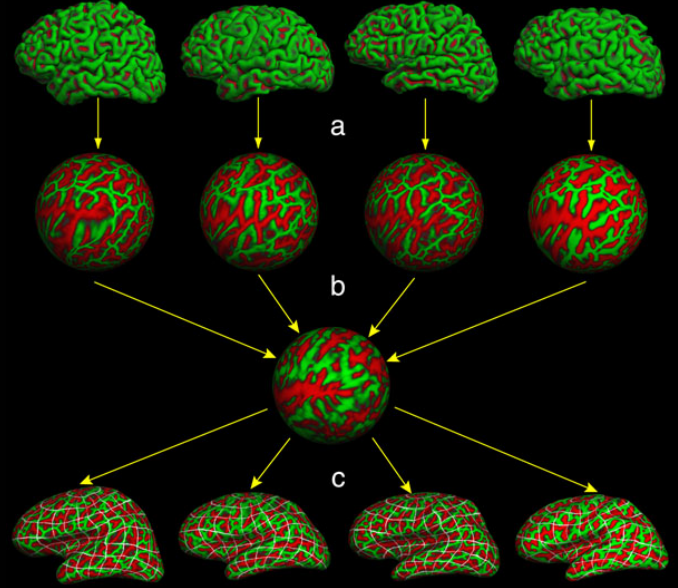
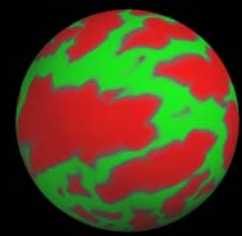
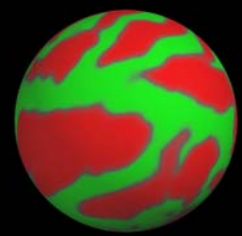


Figure 1 (above). Cortical surface reconstruction and spherical transformation (a), spherical registration of individual subjects (b), coordinate projection of registered areas onto the inflated surfaces

Figure 2 (below). Subject morphing to the average sphere target (step b from Figure 1).



Individual Subject



Average (Target)

Subject Morphing to Target

Segmentation

- Brain images were segmented with Freesurfer using a Markov Random Field (MRF) algorithm (figs. 3 and 4):
  - Calculated the probability that tissue class $C(r_i)$ occurs at spatial location r_i when tissue class $C(r)$ occurred at r
  - The segmentation was thus modeled as an anisotropic nonstationary MRF
- The volume for the both thalamic hemispheres (black arrows) was calculated for each cohort.

Statistics

- Thickness differences and mean thalamic volumes were compared using a t-test (figs. 5 and 6).
- The relationship between thalamic volume and metric distortion in each hemisphere was assessed using a generalized linear model (glm) (figs. 7 and 8).

Figure 3 (above). Segmentation of cortical and subcortical structures. After preliminary segmentation, regions are smoothed using the MRF algorithm.

Figure 4 (below). Fly through of all segmented structures.

Results

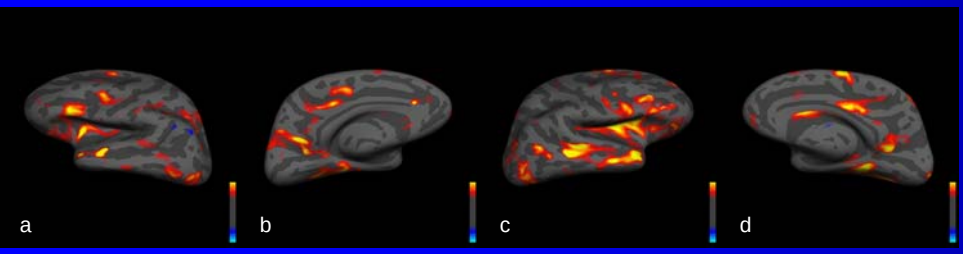


Figure 5. Cohort differences in cortical thickness (left hemisphere, a-b; right hemisphere c-d). Color bar indicates controls>schizophrenics (yellow/red) and schizophrenics>controls (dark blue/cyan). Cortical thickness differences appear to be most robust in the association and limbic cortices, particularly in the lateral right hemisphere.

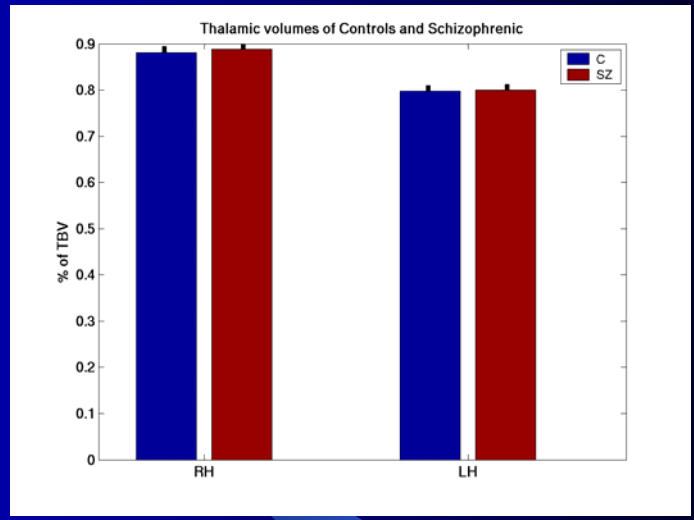


Figure 6. Bar graph showing right (RH) and left (LH) thalamic hemisphere volume for control (blue) and schizophrenic (red) cohorts (right). We found no significant difference between cohorts for either thalamic hemisphere.

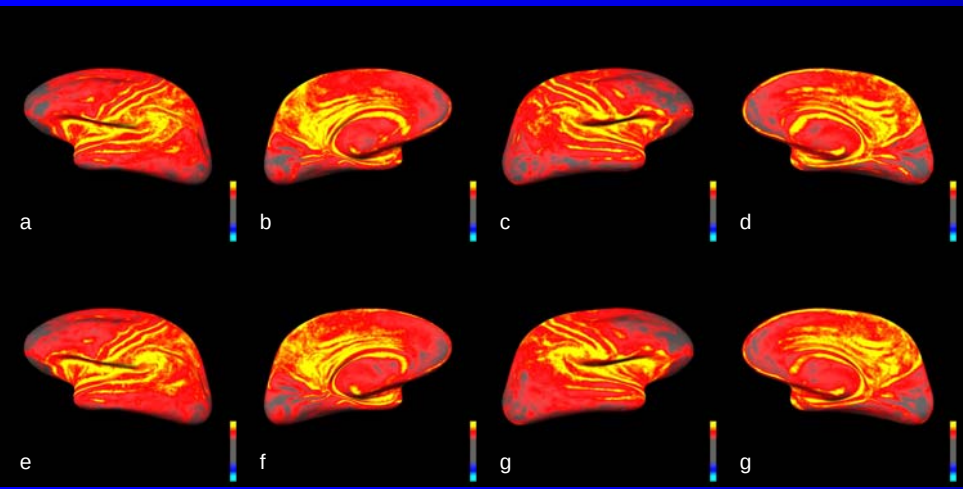


Figure 7. Mean metric distortions across the entire brain for controls (left hemisphere, a-b; right hemisphere c-d) and schizophrenics (e-h). The greatest distortion occurs in the yellow areas, and the least distortion in the red areas. Both cohorts exhibit metric distortion across the entire forebrain, but distortion is particularly high near the central sulcus and limbic areas.

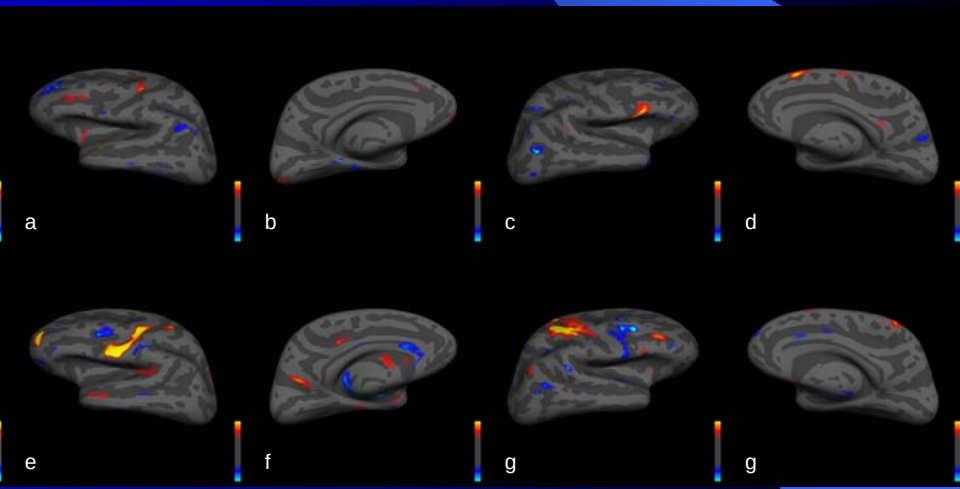


Figure 8. Generalized linear model for thalamic volume and metric distortion in controls (a-d) and schizophrenics (e-h). Color bar indicates significance range, $p<0.05$ (red/dark blue) and $p<0.01$ (yellow/cyan). A relationship between metric distortion and thalamic volume in controls is not prevalent, but in schizophrenics, a relationship appears to be strong in the central sulcus of both hemispheres, the temporal plane and the frontal pole in the left hemisphere and the ventral lateral convexity of the prefrontal cortex in the right hemisphere.

Conclusions

- The cortical ribbon appears to be thicker in the association and limbic areas (particularly in the right hemisphere) of control subjects.
- Metric distortion in the control brain was, for the most part, not related to thalamic volume
- Metric distortion in several discrete areas of the schizophrenic brain was significantly related to thalamic volume.
- In this small subset of data, thalamic volume does not appear to be significantly different between cohorts.
- Taken together, these results suggest that only subtle changes in thalamic volume may be necessary to show a significant relationship with the metric distortions required for spherical alignment, particularly near the central sulcus an in limbic areas. Thus, subtle malformations of both the thalamus and cerebral cortex in specific areas of the brain may be implicated in the pathogenesis of schizophrenia [15, 16].

Future Work

- One caveat to this work is that it only includes approximately one-third of the total number of subjects being recruited for this study. Analysis of all the subjects is necessary. Reconstruction and analysis of MPRAGE images of the remaining subjects is nearly complete.
- We will more closely analyze the relationship between cortical thickness and the underlying geometrical properties related to metric distortion.
- We will investigate the diffusion properties of the thalamocortical tracts associated with areas requiring greater metric distortion for spherical alignment.