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Data supplement

Online supplement 1

Thalamic volume assessment and results using FSL-FIRST

Whole thalamus volume assessment

Automated assessment of total thalamus volume was performed twice; once using FreeSurfer and once using the FSL-FIRST (v4.1.4) package. Thalamus segmentation using FreeSurfer and FSL-FIRST has been validated through comparison with manual tracing. Automatic segmentation by FreeSurfer is done by automatic labelling of subcortical tissue classes using an atlas-based Bayesian segmentation procedure. FreeSurfer comes with a subject-independent probabilistic atlas in Talairach space that was pre-computed from a training set of individuals whose brains were manually labelled. FreeSurfer image preprocessing steps included an affine registration with Talairach space, intensity normalisation, skull strip and a high dimensional non-linear volumetric alignment to the probabilistic atlas in Talairach space. FreeSurfer calculated the probability of a class at each voxel location as the probability that the given class appeared at that location in the training set × the likelihood of getting the subject-specific intensity value from that class. An initial segmentation was generated by assigning each point to the class for which the above probability was greatest. The neighbourhood function was then used to recalculate the class probabilities and resegment the data using the new class probabilities. This procedure was repeated until the result converged.[53] The FSL-FIRST method is a probabilistic adaptation of the active appearance model.[54] The method is informed by the shape and intensity variations of a structure from a training set for the purpose of automatically segmenting the structure. A multivariate Gaussian model of vertex location and intensity variation is used, and is based on having point correspondence across individuals (same number and labelling of vertices across individuals). The necessary correspondence is imposed during the parameterisation of the labelled images with a deformable model. The model is fit to new images by maximising the posterior probability of shape given the observed intensities. All segmentations were found to be accurate after visual inspection.

Whole thalamus volume analysis from FSL-FIRST

A main effect of diagnosis was observed for overall thalamic volumes after covarying for intracranial volume and age ($F(1,76) = 5.32$, $P = 0.02$, $d = -0.35$). No significant interactions with hemisphere were observed. That is, after correction for intracranial volume and age, individuals in the psychosis group showed a trend-level thalamic volume reduction in the left and a significant reduction in the right hemisphere (left: $F(1,76) = 3.32$, $P = 0.07$, $d = -0.29$, right: $F(1,76) = 7.43$, $P = 0.008$, $d = -0.46$). See Figs DS1 and DS2.

Additional references

53 Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002; **33**: 341–55.

54 Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage* 2011; **56**: 907–22.

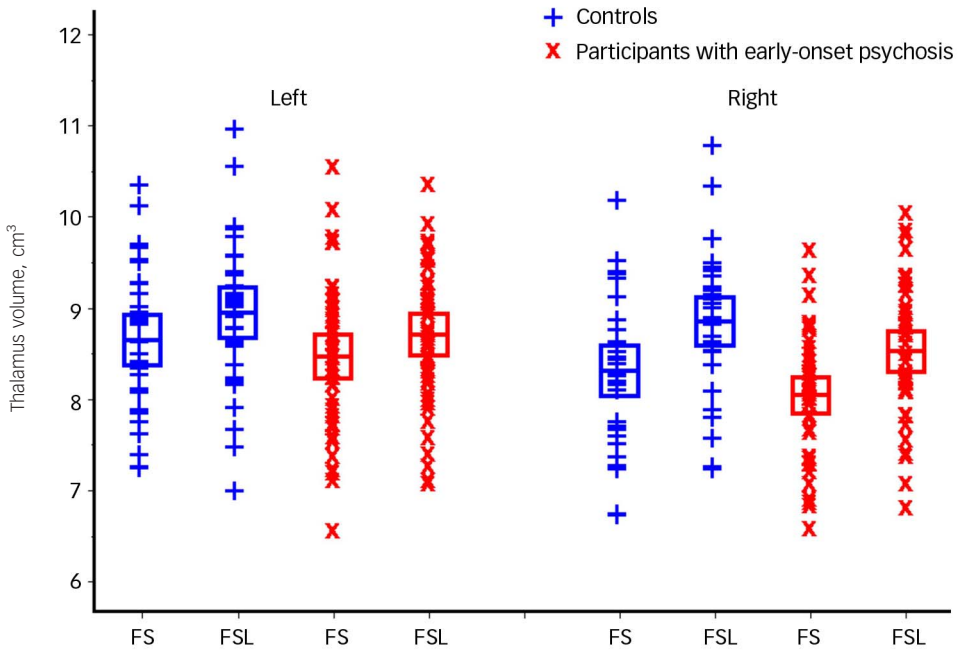

Fig. DS1 Left and right total thalamus volume of the 34 adolescent male healthy controls and 49 adolescent males with early-onset psychosis.

Values are in cm^3, the error bars represent 1 standard deviation. Thalamus volumes were obtained using FreeSurfer (FS) and FSL-FIRST (FSL) software.

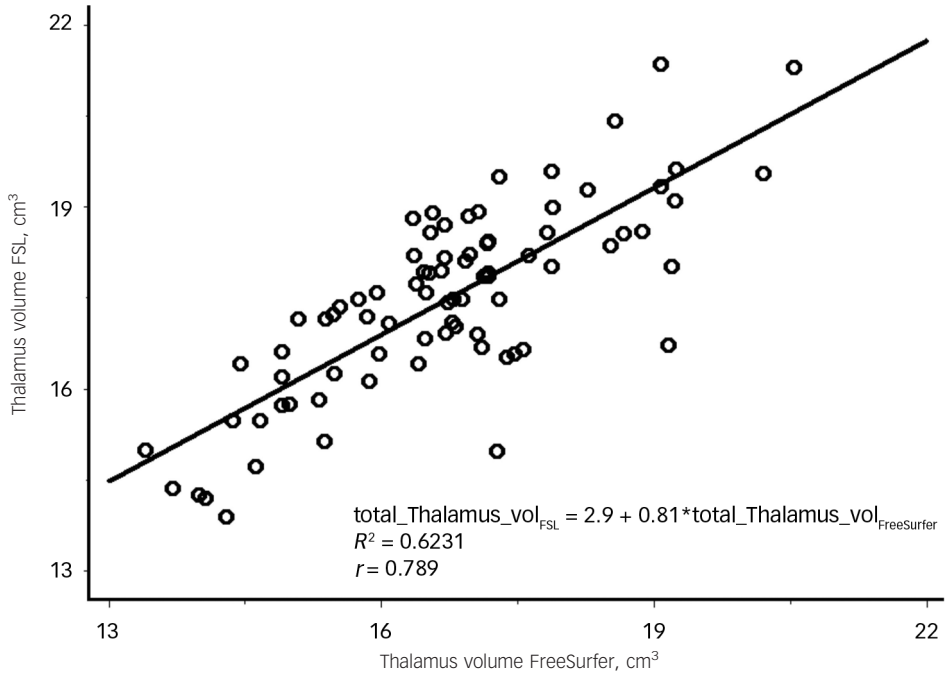

Fig. DS2 A regression plot showing total thalamus volume from FreeSurfer *v.* FSL-FIRST (FSL) data-sets, along with the correlation coefficient and regression equation relating the two sets of volumes.

Online supplement 2

Determination of an adequate combination of parameters for generating spherical harmonics (SPHARM)-based thalamic surfaces

The goal was to find an adequate combination of the three parameters that are chosen by the user (voxel resolution, SPHARM degree and subdivision level) for calculating the SPHARM-based thalamus surfaces.

The SPHARM degree determines the number of spherical basis functions that are needed to express the initial (not SPHARM-based) boundary surface meshes. If the SPHARM degree is increased, a higher number of basis functions will be used and the surface representation will be sharper. If the SPHARM degree decreases, a smoother surface representation will be obtained. The subdivision level represents the number of points of the spherical grid for the surface spherical mapping. If the subdivision level is increased, the SPHARM-based surface will have a higher number of points allowing for a better spatial representation of the initial boundary surface. In case of the thalamus, which has a smooth surface, a high subdivision level is not mandatory.

Previous studies using SPHARM to assess the shape of subcortical structures have suggested a SPHARM degree ranging from 12 to 15 and a subdivision level ranging from 10 to 20 as adequate.[55,56] To find an adequate combination of the three parameters for the current study, SPHARM-based surfaces were created using different parameter combinations within the proposed ranges. FreeSurfer assessments of the thalamus were resampled to three voxel resolutions (0.5, 0.75 and 1 mm). Five SPHARM degrees (7, 12, 13, 14, 15) and three subdivision levels (10, 15 20) were combined with the three-voxel resolution parameters. The SPHARM-based surfaces were generated in native space for each possible combination of the voxel resolution, SPHARM degree and subdivision-level parameters. For every parameter combination, the absolute distance in millimetres between the SPHARM-based surface and the initial (not SPHARM) surface was computed for each surface element. The distance was calculated as the length of the normal vector at each surface element from the SPHARM-based surface until its corresponding intersection point with the initial (not SPHARM) surface. A shorter distance reflects a good approximation of the initial (not SPHARM) surface by the SPHARM-based surface. For each parameter combination, the distance was averaged over all surface elements and over all 80 participants. This mean distance was then outlined against all combinations of the parameters (Fig. DS3).

Additional references

55 Styner M, Lieberman JA, McClure RK, Weinberger DR, Jones DW, Gerig G. Morphometric analysis of lateral ventricles in schizophrenia and healthy controls regarding genetic and disease-specific factors. *Proc Natl Acad Sci U S A* 2005; **102**: 4872–7.

56 Styner M, Lieberman JA, Pantazis D, Gerig G. Boundary and medial shape analysis of the hippocampus in schizophrenia. *Med Image Anal* 2004; **8**: 197–203.

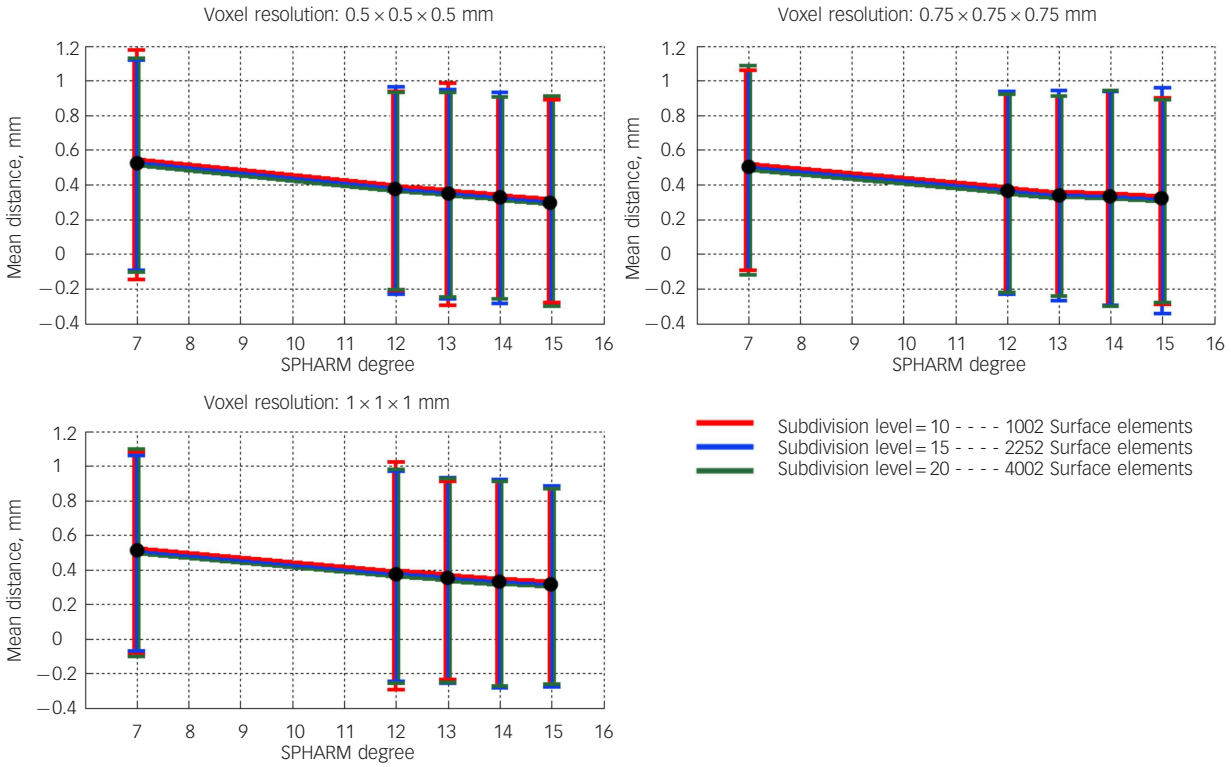

Fig. DS3 Graphs (with error bars indicating the standard deviation) showing that increasing the SPHARM degree from 7 to 12 demonstrably shortens the mean distance, suggesting that increasing the number of SPHARM basis functions will result in a better approximation of the initial (not SPHARM) surface. As can be seen, changing the voxel resolution and the subdivision level did not strongly affect the mean distance. Based on these findings, a voxel resolution of $0.5 \times 0.5 \times 0.5$ mm, SPHARM degree of 15, and a subdivision level of 10 was found to be an adequate combination of parameters for generating the SPHARM-based surfaces.

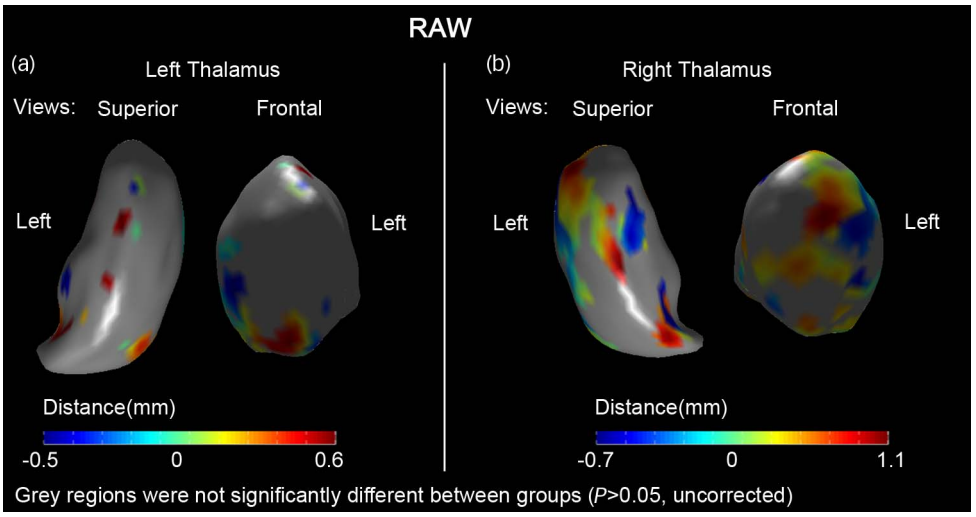

Fig. DS4 Left and right thalamus regional volumetric differences before correction for multiple comparisons between 34 adolescent male controls and 46 adolescent males with early-onset psychosis.

(a) the left superior and frontal view of the average thalamus surface of all controls and individuals in the psychosis group with a superimposed distance map. The colour bars show the magnitude and direction of the differences (distance in mm) between the average surfaces of each group obtained by SPHARM-PDM. A positive distance means that the average surface of the individuals in the early-onset psychosis group represents contraction with respect to the average surface of the controls (i.e. surface deflation of those in psychosis group) and vice versa. (b) as for (a) but for the right thalamus surface. RAW denotes uncorrected.

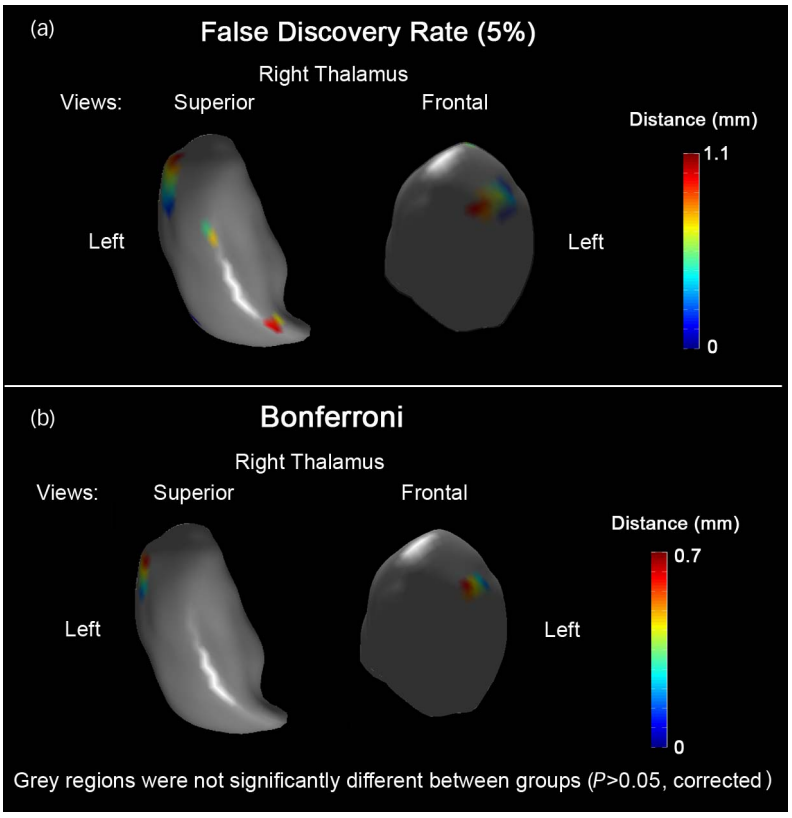

Fig. DS5 Right-sided thalamus regional volumetric differences after correction for multiple comparisons between 34 adolescent male controls and 46 adolescent males with early-onset psychosis.

(a) the right superior and frontal view of the average thalamus surface of all those in the control and psychosis groups with a superimposed distance map, after false discovery rate (5%) correction for multiple comparisons. The colour bars show the magnitude and direction of the differences (distance in mm) between the average surfaces of each group obtained by SPHARM-PDM. Anterior mediodorsal and posterior pulvinar regions showed surface deflation in the psychosis group, meaning that in this region the surface of those with psychosis showed contraction. (b) as for (a) but after Bonferroni correction for multiple comparisons.