

# Structural Abnormalities in Posterior Fossa Brain Tumor Survivors: a Voxel-Based Morphometry Study Based on Free-Form Deformation

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## Introduction

Functional MRI (fMRI) is useful to investigate brain function in survivors of childhood cancer (1), however morphological abnormalities associated with disease or treatment may interfere with spatial normalization and group comparison with healthy subjects. We recently reported altered patterns of brain activity during a continuous performance test (CPT) in children who survived posterior fossa brain tumor (PFBT) (2). These patients have surgical lesions in the cerebellum and frequently have enlarged ventricles. Region-of-interest (ROI) analysis of the fMRI data showed that the BOLD signal in patients was comparable to that in controls, but the volume of brain engaged was smaller and the location of peak activation within the ROIs was more variable. Voxel-based group analysis of patients under-represented task-induced activation in many regions. These fMRI results may indicate important disease- or therapy-induced disorganization (or reorganization) of the neural systems engaged in CPT performance, but could simply reflect errors in spatial normalization caused by systematic morphological differences.

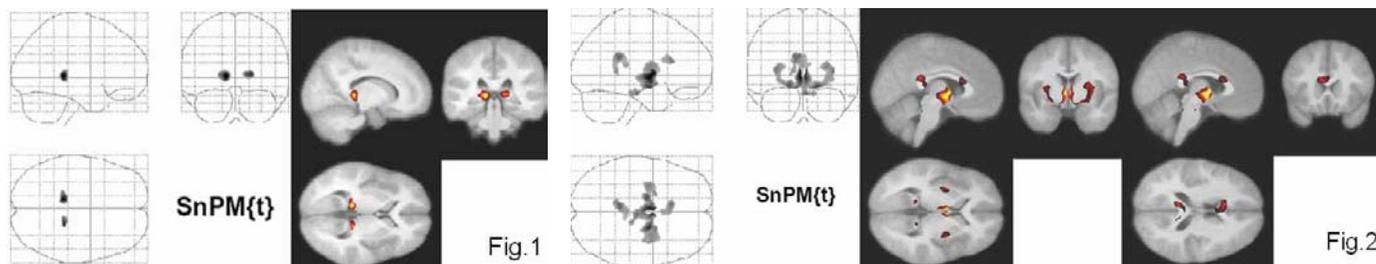
We used voxel-based morphometry (3) to test the hypothesis that focal morphological abnormalities in PFBT patients account for altered brain activation patterns during CPT performance. The standard VBM approach failed to model large focal warping of enlarged ventricles and was subject to image distortion due to the mismatch in the posterior fossa between patient images and templates. Therefore, we used Free-Form Distortion (FFD) (4) to perform spatial normalization because it offers improved local support and a similarity measure that is less susceptible to lesion-induced distortion.

## Methods

**Subjects:** Informed written consent to participate was obtained from all subjects. The patient group consisted of 13 PFBT survivors (age 12.3±3.1), 9 females and 3 left-handed according to self-report. The control group consisted of 14 healthy siblings of cancer patients (age 13.3±2.3), 10 females and 3 left-handed. **MRI:** A 1.5T Siemens Symphony scanner was used to acquire 3D T1-weighted images (MPRAGE) in the sagittal orientation with the following sequence parameters: TR, 1800 ms; TE, 2.74 ms; 15° flip angle; 128 slices, thickness 1.25 mm; FOV 210x210 mm; matrix, 512x512. **VBM:** Spatial normalization was conducted with the VTK CISC Registration Toolkit (<http://www.image-registration.com>) according to the "optimized VBM" protocol (3), and <http://dbm.neuro.uni-jena.de/vbm.html>, except that the T1 images were used instead of the gray matter segments. FFD included an affine transformation followed by a non-rigid warping to match the subjects to the ICBM 152 template. These normalized images were then averaged to create a customized high-resolution T1 template. Next, the affine and non-rigid transforms were repeated to register the raw (non-normalized) T1 images to the customized high-resolution T1 template to achieve optimized spatial normalization. Finally, the normalized images were segmented and the resulting gray matter (GM) and white matter (WM) segments were smoothed with an 8mm isotropic Gaussian kernel. We developed software to modulate the GM and WM segments by the Jacobian determinants of FFDs to reflect volume changes. **Statistical Inference:** Statistical non-Parametric Mapping (SnPM, (5) and <http://www.fil.ion.ucl.ac.uk/spm/toolbox/snpm/>) was used to conduct hypothesis testing. Statistical significance was assessed at both voxel and cluster level (family-wise error corrected threshold = 0.05) based on 500 permutations. Morphological differences are displayed as maximum intensity projections on the "glass brain" outline of the standard Talairach space (6) and on the average of normalized T1-weighted image from all subjects in the study.

## Results

FFD substantially improved the accuracy of spatial normalization in the patient group. GM density was significantly lower in PFBT survivors than in controls in bilateral thalamus (Talairach coordinates: x=-11, y=-33, z=4, voxel level p=0.002, cluster level p = 0.018 and x=20, y=-31, z=5, voxel level p=0.002, cluster level p = 0.034) (Fig. 1). WM density was also lower in PFBT survivors than in control in three regions (Fig. 2). The largest region was located at the internal capsule (x=-3, y=2, z=3, voxel level p=0.002, cluster level p = 0.002). The other two regions were identified in the corpus callosum, one at splenium (x=-7, y=-39, z=22, voxel level p=0.002, cluster level p = 0.002) and another at genu (x=-9, y=22, z=16, voxel level p=0.002, cluster level p = 0.006). Results with the modulated GM and WM segments were essentially the same as the unmodulated results (data now shown).



## Discussion and Conclusions

No morphological group differences were detected in GM where we observed altered activation in patients during the CPT. Therefore, errors in spatial normalization do not account for increased variability in the location of activation observed in these patients. The morphological differences may affect CPT activation indirectly. The pulvinar of the thalamus takes the inputs from retina, superior colliculus and secondary visual cortex and projects the outputs to parietal-occipital-temporal association cortex, and damage to the pulvinar may affect visual processing of task stimuli (letters of the alphabet). Damage to WM (Fig. 2) may affect visual processing (splenium) of stimuli and motor response (internal capsule). The fact that the results were unchanged by modulation with the Jacobian determinant suggests that the VBM reflects local abnormalities rather than artifactual changes caused by large warping around lesions or enlarged ventricles. This analysis demonstrates the utility of MRI to identify functional and structural correlates of brain injury in children treated for cancer. The functional plasticity and/or disorganization detected in PFBT survivors will help to identify the neural substrates of cognitive deficits in these patients and guide development of treatment protocols to minimize the functional impact of therapy-induced brain injury.

## References

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