Whole Brain Structural Difference between the Acute Lymphoblastic Leukemia Survivors and Healthy Siblings Using Voxel-Based Morphometry

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Introduction

Recently, we have used functional MRI (fMRI) to investigate the neural substrates of disease- and therapy-induced cognitive deficits in survivors of childhood cancer (1, 2). Comparison of brain activation during a simple continuous performance test (CPT) revealed important differences between cancer survivors and a sibling control group (2). While the peak bold signal was the same in both groups throughout the brain, the volume of tissue activated in many (but not all) regions was significantly smaller in patients. Furthermore, the location of peak activation (in standardized space) within a given region was more variable in patients than in controls. Variability of the location of activation in patients may reflect interesting functional plasticity in response to injury, or it may simply be an artifact of errors in spatial normalization caused by disease- or therapy-induced changes in brain shape. To investigate these alternative explanations, we used voxel-based morphometry (VBM) (3) to compare brain structure between survivors of acute lymphoblast leukemia (ALL) and controls. Specifically, we tested the hypothesis that there are no brain morphological differences at the locations in the brain of activation differences between these two groups during CPT performance.

Methods

Subjects: All subjects gave informed written consent to participate as approved by our institutional Office of Human Subjects Protection. The patient group consisted of 12 ALL survivors (age 10.9±2.8), 8 females, 2 left-handed (based on self report). The control group consisted of 23 healthy siblings of cancer patients (age 11.4±3.3), 15 females, 4 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; 15º flip angle; 128 slices, thickness 1.25 mm; FOV 210x210 mm; matrix, 512x512. *VBM*: Analysis was conducted with SPM2 (www.fil.ion.ucl.ac.uk/spm) according to the "optimized VBM" protocol ((3), and http://dbm.neuro.uni-jena.de/vbm.html). Briefly, a customized T1 template and gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) prior images were created using all the subjects in the study. The structural images were spatially normalized using the ICBM 152 template and then averaged. The average image was segmented, and the average and segment images were smoothed with 8mm isotropic Gaussian kernel to produce the customized T1 template and GM, WM and CSF prior images. Next, the raw (non-normalized) T1 images were registered to the customized T1 template by an affine transform, segmented based on the customized GM and WM priors, and subjected to brain extraction. The resulting gray and white matter images were normalized to the corresponding customized priors to avoid contribution from non-brain voxels and achieve optimal spatial normalization. The raw whole-brain images were renormalized according to the optimal normalization parameters, and finally the segmentation (with the customized prior images), brain extraction, and smoothing were repeated. *Statistical Inference*: Hypothesis testing was conducted using Statistical non-Parametric Mapping (SnPM, (4) and http://www.fil.ion.ucl.ac.uk/spm/toolbox/snpm/). Statistical significance was assessed at both voxel and cluster level (family-wise error corrected threshold = 0.05) based on 500 permutations. Regions of significant morphological difference are displayed as maximum intensity projections on the "glass brain" outline of the standard Talairach space (5) and on the average T1-weighted image created from all subjects in the study.

Results

No brain structural abnormalities were noted on visual inspection of the raw T1-weighted images, and *no* significant differences in the GM segments between the groups were identified in the VBM analysis. WM density was significantly *lower* in ALL patients than in controls in three regions (Fig. 1). The greatest difference was located in the left internal capsule (Talairach coordinates: x=-27, y=-14, z=31, voxel level p=0.014, cluster level p = 0.030). A region of similar shape and size, but smaller difference was identified in the right internal capsule (x=29, y=-17, z=32, cluster level p = 0.042). The third region of decreased WM density was located in the left pons (x=-10, y=-29, z=-30, cluster level p = 0.014). CSF density was *greater* in patients than in controls in the parieto-occipital sulcus, with the peak difference in the left hemisphere (x=-12, y=-82, z=35, voxel level p = 0.032, cluster level p = 0.012) (Fig. 2).

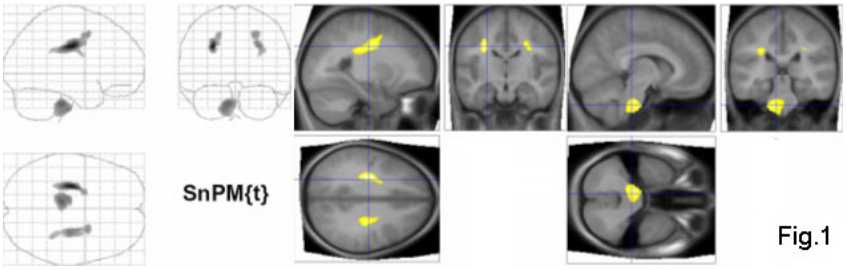

Fig.1

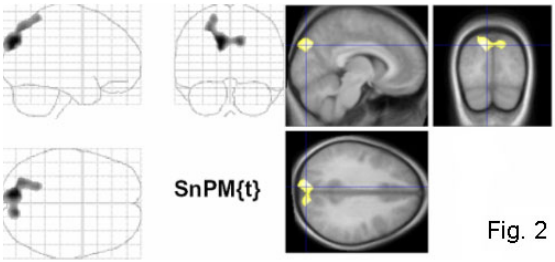

Fig. 2

Discussion and Conclusions

VBM analysis detected no differences in GM between the groups and therefore supports our hypothesis that simple errors of normalization cannot account for the increased variability in the intraregional location of sites of activation that we have noted in ALL survivors. Thus, the variability likely reflects real differences in the location of cortex engaged by patients to perform the CPT task, as compared to healthy controls. The locations of the WM differences detected between the groups imply damage to corticopontine projections that are a critical feed-forward element of the cerebrocerebellar system (6). The fact that the WM differences were so well defined anatomically indicates that the corticopontine projections may be particularly vulnerable to CNS therapy for ALL (intrathecal methotrexate). The left lateralization of the corticopontine lesions suggests that there may be some interaction between WM toxicity and motor dominance or language lateralization. The CSF 'lesion' appeared at approximately the same transverse level as the white matter regions, and we interpret this as expansion of the parieto-occipital sulcus in reaction to atrophy in the internal capsule. Further studies will be required to validate and elaborate these findings, however this study highlights the value of voxel-based morphometry to facilitate the interpretation of functional imaging findings and to identify potentially important morphological abnormalities in clinical populations.

References

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