Brain morphometry using diffusion-weighted magnetic resonance imaging: application to studying subjects at high genetic risk for schizophrenia

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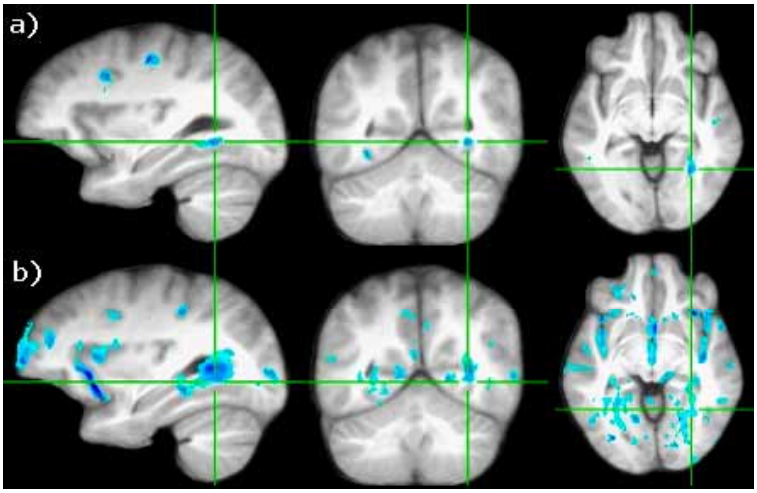
Background: An understanding of the biological predictors for developing schizophrenia will provide valuable information about the etiology of the illness and allow early treatment that could improve the prognosis for this devastating disorder. In this abstract, a recently proposed method for assessing cortical atrophy based on the apparent diffusion coefficient (ADC) (Ardekani et al., 2005a) is applied to studying subjects at high genetic risk of developing schizophrenia. The innovation of this method is the assertion that ADC may be used as an endogenous marker of cortical volume deficits.

Methods: MRI scans were performed on a 1.5T Siemens Vision system (Erlangen, Germany). Image sequences acquired included: a magnetization-prepared rapid gradient echo (MPRAGE) image (TR/TE=11.6/4.9 ms, flip angle 8°, 172 slices, 1.20 mm thick, 307mm FOV, 256×256 matrix size, 8/8 Rect. FOV, 1.20×1.20 mm^2 pixel size), a dual spin echo image (TR 5000 ms, TE 22/90 ms, 24 slices, 5 mm thick, no skip, 1 average, 190×256 matrix size with 6/8 reduced FOV, flip angle 180°, 224 mm FOV, pixel size=0.88×0.88 mm^2), and diffusion weighted images (TR 6000 ms, TE 100 ms, 128×128 matrix, 320 mm FOV, 8/8 Rect. FOV, b-value=1000 s/mm^2, 8 non-collinear gradient orientations, 7 averages, 19 slices, 5 mm slice thickness, no skip, pixel size 2.5×2.5 mm^2). A data set of 25 controls (mean age±SD: 25±4.5 years), 15 patients with schizophrenia (mean age±SD: 34±10.6), and 12 subjects at high genetic risk for schizophrenia was analyzed (mean age±SD: 25±4.1 years).

Analyses: For group analysis purposes, the MPRAGE image of each subject was spatially normalized to a standard space. MPRAGE images were first automatically skull stripped using the FreeSurfer software package (Segonne et al. 2004). Then, the striped MPRAGE images were spatially normalized to a template image in Talairach and Tournoux space using a non-linear 3D warping algorithm (Ardekani et al. 2005b). In this process, the MPRAGE image was iteratively warped to match the template image using a multi-resolution approach that uses the cross-correlation cost function as a measure of registration accuracy. The non-linear transformation determined by the program was approximated as a truncated Fourier-Legendre series and saved as a warp field. Next, the MPRAGE volume was registered to the T2 volume using a linear rigid-body transformation. The transformation for this registration was computed by first obtaining a matrix, which transforms the MPRAGE volume to same orientation and FOV as the T2 volume. The image obtained from the previous step was then registered to the T2 volume using an iterative linear registration program, this program basically corrects for small registration errors due to subject motion. The transformation obtained from this step was pre-multiplied to the first matrix to obtain the resultant rigid-body transformation. To correct for distortion, the DTI volume obtained without diffusion weighting (b=0) was re-sliced to the same size as the T2 volume and then warped to a skull striped T2 image using a non-linear 2D warping algorithm. This algorithm is the 2D version of the algorithm used in the intersubject registration step. The resulting warp fields were saved. From the eight DTI volumes acquired with diffusion gradients and one without diffusion gradient, the diffusion tensor D was estimated for each voxel on the basis of the method described by Basser et al. (1994). The diffusion tensor D, is expressed as a 3×3 matrix and has six independent elements. The ADC was computed as the average of the eigenvalues λ_1, λ_2, *and* λ_3 of the diffusion tensor D as follows: $ADC=(\lambda_1+\lambda_2+\lambda_3)/3=trace(D)/3$. Finally, all three transformations described above (3D non-linear warping, rigid-body, and 2D non-linear warping) were combined mathematically into a single transformation and applied to the ADC map using a tri-linear interpolation to obtain ADC maps that are distortion corrected and spatially normalized. The ADC maps were generated for all subjects. To assess the differences between the ADC maps of schizophrenic patients and controls, and subjects at high genetic risk for schizophrenia and controls, two-tailed voxel-wise independent samples student's t-tests were used. The obtained t-map was then thresholded to find voxels, where the ADC values significantly differed between the groups. To reduce the false-alarm rate, only clusters of size 200 mm^3 or greater in the thresholded image were retained.

Results: Four regions were identified in which subjects at high genetic risk with schizophrenia and patients had increased ADC. These included regions in the vicinity of the left parahippocampal gyrus, right superior temporal gyrus, left superior frontal gyrus, and left middle frontal gyrus. These data indicate that subtle cortical atrophy may already be occurring in people at high-risk for developing schizophrenia prior to actually showing clinical signs of the illness. The ADC may be a particularly sensitive way of determining who is beginning to develop atrophy. Future longitudinal studies will clarify its predictive value.



The Figure on the left represents regions where subjects at high genetic risk for schizophrenia (n=12) and patients (n=15) had significantly ($p<0.01$, cluster size >200 mm^3) higher (shown in blue) apparent diffusion coefficient (ADC) than controls (n=25). Regions are superimposed on the average intersubject registered MPRAGE from all participants. Cross-hairs in (a) and (b) represent sagittal, coronal, and axial views of the region in the vicinity of the left parahippocampal gyrus, where ADC was higher in both patients (b) and subjects at high genetic risk for schizophrenia (a).

References:

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