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Early detection of schizophrenia by diffusion weighted imaging

Lynn E. DeLisi[a,b,*], **Kamila U. Szulc**[b], **Hilary Bertisch**[b], **Magda Majcher**[a], **Kyle Brown**[a], **Arthika Bappal**[a], **Craig A. Branch**[a,c], and **Babak A. Ardekani**[a,b]

a*The Nathan S. Kline Institute for Psychiatric Research, Department of Medical Physics, 140 Old Orangeburg Road, Orangeburg, NY 10962, USA*

b*The New York University School of Medicine, Department of Psychiatry, 650 First Avenue, New York, NY 10016, USA*

c*Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA*

Abstract

A novel magnetic resonance imaging method was used to determine whether it is feasible to detect early signs of cortical atrophy among individuals who are at high risk for developing schizophrenia. Fifteen individuals at high-risk for schizophrenia and 15 of their first degree relatives diagnosed with schizophrenia were compared with controls ($n = 25$) who did not have a family history of psychiatric illness or psychiatric hospitalizations. On the basis of a voxelwise analysis of apparent diffusion coefficient (ADC) maps derived from diffusion weighted magnetic resonance imaging, these individuals showed evidence of deficits in four separate regions of the brain, all on the left side only: parahippocampal gyrus, lingual gyrus, superior frontal gyrus, and middle frontal gyrus. However, conventional volumetric quantification of ventricular space to detect atrophy failed to reveal differences between high-risk subjects and controls. It is concluded that ADC may be a more sensitive measure than ventricular volume assessments for use in future studies of early prediction of schizophrenia.

Keywords

MRI; Diffusion Tensor Imaging; Apparent Diffusion Coefficient; Morphometry; Prodrome; Atrophy

1. Introduction

Schizophrenia is a neuropsychiatric disorder that at least in its chronic stages shows detectable evidence of brain structural abnormalities in the majority of afflicted individuals (Shenton et al., 2001). Ventricular enlargement and cortical atrophy have long been recognized complications of schizophrenia (Jacobi and Winkler, 1927;Johnstone et al., 1976;Weinberger et al., 1979a). Some studies have also shown that these changes are present by the time of the first episode of illness, but to a lesser extent (Weinberger et al., 1979b). A few studies exist of brain structure in people at ultra-high-risk for schizophrenia; they report inconsistent regional cortical changes before illness onset, with progressive changes in those who eventually develop illness, and fail to detect evidence of atrophy or increased brain cerebrospinal fluid (CSF) (Lawrie et al., 2002;Pantelis et al., 2003;Job et al., 2005). A recently published and novel diffusion weighted magnetic resonance imaging (DW-MRI) method for voxelwise analysis of the apparent diffusion coefficient (ADC) could be a more sensitive measure for assessing early appearing cortical atrophy (Ardekani et al., 2005). The premise that ADC can be used as a

* Corresponding author. The Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962, USA. Tel.: +1 845 398 5471; fax: +1 845 398 5472. *E-mail address:*DeLisi76@AOL.com (L.E. DeLisi).

surrogate for volume deficit is novel. Ardekani et al. (2005) used voxelwise analysis of ADC maps to identify cortical regions with volume deficits. The method relies on the assumption that reductions in brain volume are accompanied by commensurate increases in the local volume of CSF. Because the ADC of CSF is greater than that of brain parenchyma, one can expect an increase in ADC in regions with volume deficit in voxelwise group analyses. In effect, CSF acts as an endogenous tracer for measuring cortical gray matter loss using diffusion tensor imaging. Ardekani et al. (2005) showed that above-normal ADC could be found in multiple brain regions in schizophrenia where previous studies had demonstrated tissue atrophy.

The present study has thus applied this method to individuals at high risk for developing schizophrenia compared with their siblings who have chronic schizophrenia and controls in order to determine whether this approach might provide an early marker for schizophrenia. An understanding of the biological basis for why individuals are at high risk for developing schizophrenia is likely to provide valuable information about whether early treatment should be instituted to improve the prognosis for this devastating brain disorder.

2. Methods

2.1. Subjects

Individuals were recruited for this study if they had a first degree relative with schizophrenia. Both those family members with schizophrenia and those who were not diagnosed with a psychotic disorder but who were still in the peak age of risk for schizophrenia (defined as ages 12–30 and thus defined as high risk) were recruited for this study. Seventeen independent nuclear families participated, in six of which only one high-risk subject completed the study and no relative with schizophrenia. Of the remaining 11 families, one consisted of three individuals with schizophrenia (2 affected sibling pairs and 1 schizophrenia/high-risk sibling pair who are cousins), one consisted of two high-risk and two schizophrenia siblings, two were affected sibling pairs, one contributed four high-risk siblings, two were discordant sibling pairs (one with schizophrenia and one at high risk). Four subjects with schizophrenia did not have any of their other family members participate in this study. Thus these family members were categorized as either individuals with schizophrenia (n = 15; 12 males; mean age = 34.27 ± 10.67 years; age range: 20–55 years), or as individuals at high risk to develop the illness (n = 15; 6 males; mean age = 19.27 ± 4.64 years; age range: 13–27) (Table 1). None of the controls or high-risk subjects were on antipsychotic or antidepressant medications. Of the 15 subjects with schizophrenia, 13 were medicated with atypical antipsychotics, while two were unmedicated.

Families were recruited by placing advertisements in newspapers and newsletters distributed by multiple chapters of the National Alliance for the Mentally Ill (NAMI). In addition, families who previously participated in other genetic studies on schizophrenia conducted by the principal author were contacted for eligibility for the current study (DeLisi et al., 2002). Controls (n = 25; 9 males; mean age = 23.72 ± 3.73 years; age range: 17–30 years) were solicited from the community by advertisement and were eligible for participation if they had no family history of any psychotic disorder, psychiatric hospitalization, or suicide in a first or second degree relative. Controls were not included if, on evaluation, they were found to have evidence of a psychotic illness (schizophrenia, bipolar disorder or psychosis not otherwise specified).

This study received Institutional Review Board Approval for human subjects research at the Nathan S. Kline Institute and at New York University School of Medicine. All subjects gave written informed consent for their participation after careful explanation of the nature of the study and its procedures.

2.2. Image acquisition

MRI scans were performed on a 1.5 T Siemens Vision system (Erlangen, Germany). Image sequences were acquired in a standard orientation and included: a 3D magnetization-prepared rapid gradient echo (MPRAGE) image (TR/TE = 11.6/4.9 ms, flip angle 8°, 172 slices, 256×256 matrix size, 1.20×1.20×1.20 mm^3 voxel size), a T2-weighted spin-echo image (TR/TE = 5000/90 ms, 24 slices, 5 mm slick thickness, no gap, 256×256 matrix size, 0.88×0.88 mm^2 pixel size), diffusion weighted images obtained by echo-planar imaging (EPI; TR/ TE = 6000/100 ms, *b*-value = 1000 s/mm^2, 8 non-collinear diffusion sensitizing gradient orientations, 7 averages, 19 slices, 5 mm slice thickness, no gap, 128×128 matrix, pixel size: 2.5×2.5 mm^2), and one EPI volume without any diffusion sensitizing gradients ($b = 0$).

2.3. Image processing

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 (Fischl et al., 1999). Then, the stripped MPRAGE images were spatially normalized to a template image in Talairach and Tournoux (Talairach and Tournoux, 1988) space using a non-linear 3D warping algorithm. 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 represented as a truncated Fourier–Legendre series. 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 that transforms the MPRAGE volume to the same orientation and FOVas the T2 volume. This reoriented MPRAGE volume is then registered to the T2 volume using an automatic linear registration program, which essentially corrects for any residual small registration errors in the MPRAGE volume relative to the T2 volume. The final transformation matrix for matching the MPRAGE and T2 volumes is obtained by calculating the matrix product of the two matrices, i.e., one that corrects for differences in orientation (sagittal to axial) and one that corrects for possible residual motion.

To correct for EPI distortion, the volume obtained without diffusion weighting ($b = 0$) was non-linearly matched to the skull stripped T2 image set using a 2D warping algorithm. This algorithm is a 2D version of the algorithm used in the intersubject registration step employed in the MPRAGE intersubject registration. The deformation field from this step was also saved. Finally, the two non-linear and one linear transformations described above were mathematically combined into a single displacement field that can be used to match any spatial location in the standard Talairach and Tournoux space to the corresponding point in space of the DW-MRI data.

From the seven volumes acquired with diffusion sensitizing gradients and the $b = 0$ volume, a diffusion tensor *D* was estimated for each voxel on the basis of the method described by Basser (1995). The ADC was computed as trace (*D*)/3. The ADC maps were generated for all subjects and transformed to the standard space using the registration process described above.

To assess the differences between the ADC maps of patients with schizophrenia and controls, and subjects at high genetic risk for schizophrenia and controls, voxelwise analyses of covariance (ANCOVAs) controlling for age and sex were used. By contrasting between groups, a Student's *t* statistic was computed at each voxel. The obtained *t*-map was then threshold at $P<0.01$ 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.

For volumetric measurements of the lateral ventricles and whole brain, the 3D Slicer software package (http://www.slicer.org; freely available, open-source software) was used on T1-weighted MPRAGE images for computer assisted manual segmentation (measurement reliability of ICC: 0.99 for both sets of measurements). Whole brain measurements included both the cerebellum and lateral ventricles. These data were analyzed for group differences (high-risk subjects, patients with schizophrenia, and controls) using an ANCOVA controlling for whole brain size, age, and sex.

3. Results

Four regions were identified in which subjects at high genetic risk for schizophrenia and patients with schizophrenia had increased ADC at $P<0.05$ when co-varying the analyses for age and sex. These included regions in the vicinity of the left parahippocampal gyrus, left lingual gyrus, left superior frontal gyrus, and left middle frontal gyrus (Fig. 1). However, when the threshold was increased to $P<0.01$, only the left middle frontal gyrus difference remained significant for both groups. One region of low ADC appeared in the schizophrenia subjects compared with controls in the region of the body of the corpus callosum (Fig. 1a). This did not appear in the high-risk subjects and was not present at the $P<0.01$ level. No other regions showed significantly lower ADC in either group.

When controlling for whole brain volume, age, and sex there were significant differences between groups in both total left and right ventricular size (Table 2) (right ventricle: $P<0.001$; left ventricle $P<0.004$) manifested by significant ventricular enlargement in the patient group compared with controls (right ventricle: $P<0.001$; left ventricle: $P<0.003$). Individuals at high risk for schizophrenia also had a significant difference in ventricular size compared with controls in both left and right ventricular size (right ventricle: $P<0.008$; left ventricle: $P<0.020$). Individuals at high risk for schizophrenia had no difference in ventricular size compared with controls.

4. Discussion

Schizophrenia is a progressive and chronic brain disorder (DeLisi, 1999) that if detected early may be treated in a rigorous manner so that the severe consequences of its chronicity are attenuated. Thus, methods that are sensitive to early biological changes caused by the development of this illness could have predictive value in the future for the institution of early treatment. Since MRI has been a useful tool for detecting structural brain changes in individuals with schizophrenia, a new method was employed in the present study to determine whether it would provide additional sensitivity to detect early brain changes not seen using conventional volumetric analyses of these scans.

The results of this study show that analysis of ADC maps derived from diffusion weighted MRI data may be able to detect early regional brain deficits in individuals who do not now have symptoms of schizophrenia, but who are at high risk to develop such symptoms, as compared with low-risk controls. It also can be seen that patients who have chronic schizophrenia show more extensive differences from controls than their high-risk siblings, suggesting that progression to further brain changes occurs with the chronic clinical illness.

The ADC changes observed here likely represent changes in the amount of CSF occupying ventricular as well as interstitial brain space, although the exact interpretation of these data may depend on the model employed to interpret the underlying diffusion phenomena (Szafer et al., 1995;Meier et al., 2003). Nonetheless, the increased ADC seen in the subject at high risk for schizophrenia and those with schizophrenia indicates that an atrophic process may be

occurring. Further longitudinal research with larger cohorts of high-risk individuals is needed to determine whether ADC will be a useful tool for early detection of schizophrenia.

The limitations of this study are important to note. First, the numbers of subjects are small in each group and although all analyses were co-varied for age and sex, matching for these variables was not possible. It is probable that the disappearance in all but one of the regions of difference at the $P<0.01$ level of significance was due to the small number of individuals in each cell when co-varying for age and sex. Another limitation to the study design is that several of the schizophrenia and high-risk subjects were biologic relatives and the contribution of inheritance to variation in structural size and the ADC was not accounted for in the analyses. In addition most of the subjects who had schizophrenia were medicated, while all other subjects were not; thus whether medications could cause the differences could not be determined. Finally, the method for analysis attempted to reduce the false-positive discovery rate, but it is still unknown whether the changes we report could be chance findings. In summary, this was an initial study using a novel technique to determine whether it could be usefully applied toward early detection of schizophrenia. Future studies are now needed to expand upon these preliminary findings.

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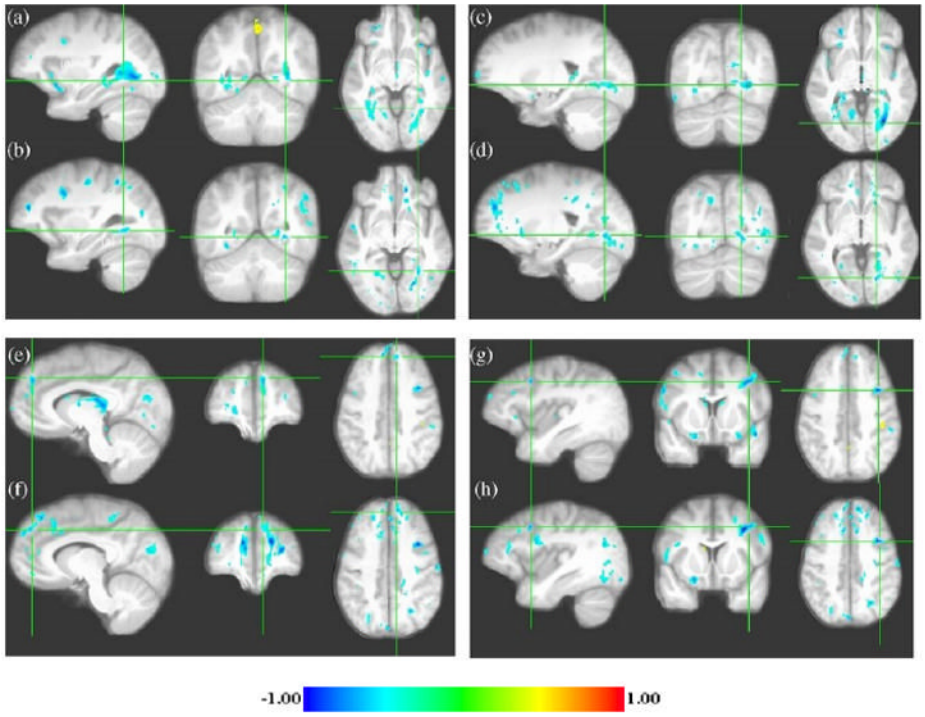

Fig 1.

Brain regions where subjects at high genetic risk for schizophrenia (n = 15) and subjects with schizophrenia (n = 15) had significantly (P<0.05, cluster size>200 mm^3) higher (shown in blue) apparent diffusion coefficient (ADC) than controls (n = 25). Images from each group are superimposed on the average intersubject registered MPRAGE from all participants. (a), (c), (e) and (g) reflect regions showing significant increases (after correction) of ADC in patients with schizophrenia compared with controls, and similarly (b), (d), (f) and (h) show significant differences of ADC in individuals at high risk for developing schizophrenia compared with controls. The cross-hairs indicate sagittal, coronal, and axial views of each region for the following regions with similar differences in both groups: (a) and (b) indicate a region in the vicinity of the left parahippocampal gyrus (Talairach coordinates: -28[L],-52[P],-4[I]). (c) and (d) indicate a region in the vicinity of the left lingual gyrus (Talairach coordinates:-21[L],-66 [P],-2[I]). (e) and (f) indicate a region in the vicinity of the left superior frontal gyrus (Talairach coordinates:-9[L], 46[A], 36[S]). (g) and (h) indicate a region in the vicinity of the left middle frontal gyrus; Talairach coordinates: -35[L], 10[A], 39[S]).

Table 1

Demographic characteristics of subjects

	Age (mean ± S.D.)	Male	Female
High-risk subjects (*n* = 15)	19.27 ± 4.64	6	9
Subjects with schizophrenia (*n* = 15)	34.27 ± 10.67	12	3
Controls (*n* = 25)	23.72 ± 3.73	9	16

Table 2

Mean (±standard deviation) ventricular and whole brain volumes for individuals at high genetic risk for schizophrenia, their family members with schizophrenia, and controls

	Left ventricle	Right ventricle	Whole brain volume
High-risk subjects (n = 15)	4.95 ± 1.04	4.59 ± 1.34	1380.27 ± 135.67
Subjects with schizophrenia (n = 15)	11.47 ± 6.01	10.95 ± 5.59	1418.73 ± 77.12
Controls (n = 25)	5.48 ± 2.21	4.89 ± 1.84	1383.25 ± 109.05
$F(\nu^1, \nu^2)$	6.192 (2, 48)	8.172 (2, 48)	0.82 (2, 49)
$P <$	0.004*	0.001*	0.922

Controlling for age, sex, and whole brain volumes, left ventricles were significantly larger in the subjects with schizophrenia relative to controls (P<0.003), as well as relative to those with a high genetic risk for schizophrenia (P<0.020). Also, controlling for the same factors, right ventricles were significantly larger in the subjects with schizophrenia relative to controls (P<0.001), as well as relative to those with a high genetic risk for schizophrenia (P<0.008). There was no significant difference in brain volume when controlling for age and sex in the analysis.