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SHORT COMMUNICATION

ADC changes in schizophrenia: a diffusion-weighted imaging study

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Abstract Studies using diffusion tensor imaging (DTI) have shown multifocal reduction in anisotropy of white matter fibre tracts in schizophrenia, and a few of these also suggest changes in apparent diffusion coefficient (ADC). In this study, we assessed ADC in 18 patients with schizophrenia and 18 healthy controls using a voxel-based approach. We did not find evidence of statistically significant changes in ADC in either direction at $P < 0.05$ (FDR corrected) using different smoothing filter sizes; only at an uncorrected threshold of $P < 0.001$ did we find an increase in a small right prefrontal area close to our previous FA finding. Our findings therefore do not support ADC changes to be a marker of white matter or grey matter abnormalities in schizophrenia. Changes in other parameters like fractional anisotropy (FA) might be a more sensitive indicator of white matter pathology in this disorder.

Keywords Schizophrenia · Brain · Magnetic resonance imaging (MRI) · Diffusion tensor imaging (DTI) · Apparent diffusion coefficient (ADC)

Introduction

Diffusion-weighted imaging has been applied to study white matter pathology in schizophrenia. Studies using diffusion tensor imaging (DTI), which assesses multiple aspects of molecular diffusion, have mostly focussed on parameters such as fractional anisotropy (FA). These studies have repeatedly shown multifocal FA reductions in frontal and callosal, but also temporal and parietal white matter regions [9]. However, DTI scans might be analysed with respect to other informative parameters describing microstructural properties.

The apparent diffusion coefficient (ADC) is a parameter derived from diffusion-weighted MR images, which describes basic diffusion properties of the tissue [17]. It is sensitive to changes in cell volume (e.g. cell swelling) and has widely been used in the study and clinical assessment of stroke, since perfusion deficits can ultimately result in ischaemic depolarisation, cell swelling and neuronal death [18].

Several studies have suggested that schizophrenia might involve regional ADC increase as well, although quantitatively far more subtle. This has been suggested for regions-of-interest (ROI) analyses of the corpus callosum [5], as well as frontal and temporal cortical areas [16], whereas other studies have suggested multifocal involvement [1, 3, 4]. Our present study was designed to extend findings of the above studies using voxel-wise resolution and an observer-independent methodology. Also, we intended to use ADC as an indicator, which reflects more basic properties of cellular pathology, especially in the white matter, which is otherwise difficult to study with MR.

Methods

We analysed the apparent diffusion coefficient (ADC) in a cohort of 18 DSM-IV schizophrenia patients (mean age

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29.6a ± 7a; 4 females/14 males) and 18 healthy controls (mean age 29.0a ± 10a; 6 females/12 males), matched for age, gender and handedness. We have previously reported analyses of an fMRI study as well as fractional anisotropy measures (derived from DTI scans) in this cohort [15], in which we found FA reductions in the right medial temporal lobe and frontal lobe white matter. Patients were scanned while in remission from a psychotic episode and stabilised on neuroleptic medication (mean PANSS score: 69.4 ± 23.7; $n = 16$). The ethics committee of the Friedrich-Schiller-University of Jena approved the study protocol, and all participants gave written informed consent.

As described previously [15], we obtained for each subject a diffusion tensor imaging (DTI) data set on a 1.5 Tesla Siemens Magnetom Vision plus scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard CP transmit/receive coil (TRSE-EPI sequence, TR 4000 ms, TE 100 ms; one b_0 image and six diffusion-weighted images in independent directions, with $b \approx 940$ s/mm^2). Two volume sets of 19 axial slices each (3-mm-slice thickness and 3-mm gap, in-plane resolution 2.5 mm × 1.88 mm, matrix 96 × 128, interpolated to 256 × 256) were acquired sequentially, shifted by 3 mm along the z-axis. When merged, these covered the cerebrum and upper cerebellum. Images were visually inspected for movement-related mismatch between the two scan volumes.

We analysed data using the SPM software package (Institute of Neurology, London, UK) as well as internal software for calculation of ADC. The ADC was computed in every voxel of the image. In order to compare the ADC maps across groups, we applied a two-step normalisation using SPM2. First, we computed a b_0 template using the individual b_0 images, to which we applied a 12-parameter affine co-registration, re-slicing to 3 × 3 × 3 mm^3 isotropic voxels, and averaging. For smoothing, we used a 6-mm FWHM Gaussian kernel. Each individual b_0 image was normalised to this template (12-parameter affine transformation and then non-linear normalisation with 6 × 8 × 6 basis functions) to apply the individual transformation parameters to the ADC maps (mean of the eigenvalues in each voxel).

For statistical analysis, we tested both reductions and elevations of ADC in patients with a voxel-wise analysis using a general linear model and thresholds of $P < 0.05$ with FDR correction for multiple comparisons.

Results

We did not detect any significant differences in ADC between the two groups at the $P < 0.05$ FDR corrected threshold, i.e. neither increases nor decreases in ADC in patients.

Based on previous findings suggesting a dependency of filter size in DTI studies [8], we performed post hoc analyses using filters of 4- and 8-mm FWHM, respectively. However, there was no significant result with either of these two filters. In an additional exploratory analysis, we applied a lower threshold to the original analysis with an uncorrected level of $P < 0.001$, resulting in a few scattered clusters of ADC increase in patients, including a right lateral prefrontal lobe cluster, close to our initially reported finding of reduced fractional anisotropy [15].

Discussion

Our study failed to demonstrate changes in ADC in schizophrenia, even with the use of different filter sizes aiming to account for effects of different spatial extent. Thus, we did not replicate earlier findings of ADC increase in the corpus callosum [5] or frontal and temporal cortices [13, 16]. Beside mere methodological differences to previous studies, there are several important physiological factors meriting consideration in ADC studies in schizophrenia.

The underlying physiology of ADC changes in humans, although not completely understood, is of potentially great interest in brain disorders like schizophrenia. This is particularly the case for the study of white matter abnormalities, since ADC adds interesting and relevant information to conventionally used FA. The ADC depends on several aspects of tissue microstructure, including the diffusion across membranes and the tortuosity of extra-cellular space, influenced by extracellular matrix molecules [18]. Other microscopic features include the relation of ADC to electrical conductivity [17] and aspects of neurotransmission such as volume transmission [18]. While the basis of ADC changes in schizophrenia remains incompletely understood, the physiology of the marker makes it highly attractive to complement data derived from other modalities and markers, e.g. FA and fibre tract tracing. A clear distinction, however, must be made between the use of ADC for white matter as opposed to grey matter abnormalities, as this possibly reflects completely different underlying cellular pathologies. So far, ADC data in schizophrenia are inconsistent for either application, in particular for white matter.

As our findings fail to support the presence of large ADC pathology in schizophrenia, it is worthwhile noting the heterogeneity of the current literature on this parameter. While initial positive findings have suggested pathologies of the corpus callosum [5] and possibly fornix [4], only a minority of these findings have been replicated [13], while other findings either have not yet been independently replicated [1] or show conflicting findings, such as for

cerebellar structures [11, 19]. A few studies have also computed measures such as mean diffusivity (MD), which is closely related to ADC. These have shown increases in mean diffusivity in the splenium (but not genu) of the corpus callosum of chronic patients [7], a finding not replicated in first-episode patients [12]. More recent studies have shown MD to be elevated in the fornix [10], but not the cerebellar peduncles [11, 19]. Most of these investigations have used region-of-interest approaches, and only a most recent study applied a voxel-wise approach identifying widespread frontal, temporal and parietal cortical increases in MD [14]. Also, ADC has been suggested as a surrogate marker for cortical atrophy in multiple regions [4].

All these studies vary substantially in their methodology (ROI vs. voxel-wise comparisons, normalisation/registration used in the voxel-based studies, number of subjects included, clinical status, etc.), and even when considering the ADC and MD studies together, there is no clear pattern emerging yet for white matter, and a possible suggestion only for frontal and temporal cortical changes [4, 16]. In our study, none of these changes were confirmed, despite the use of an optimised normalisation algorithm, exclusion of interactive (and thus user-dependent) operations, and even post hoc application of different smoothing filter sizes [8]. Voxel-based methods, however, might be more prone to registration errors, which might be particularly relevant to the border between grey and white matter and in regions where normalisation algorithms achieve imperfect alignment between subjects (including cortical areas of high anatomical variability). In the latter cases, ADC difference might emerge as a function of misregistration and indicate regional cortical atrophy rather than qualitative pathology [4, 16]. In fact, earlier use of ADC in some studies with schizophrenia patients was aimed at the assessment of cortical atrophy rather than qualitative changes in brain tissues [4].

Finally, we need to consider some limitations of our study. First, the sample size might have limited our ability to detect more subtle ADC changes. Second, our patients were on stable antipsychotic medication, which might have affected results, given that medication might ameliorate or otherwise influence ADC changes [2]. Third, we need to consider state-dependent effects on ADC and related parameters, as have been demonstrated in a recent study in bipolar disorder [20]. Given our patient selection, we cannot infer on the timing of these changes across the disease course or regionally different effects in first-episode vs. chronic patients.

In summary, our lack of positive findings in this carefully selected and fairly homogenous patient sample (with respect to disease stage and clinical state) does not support ADC pathology in schizophrenia. While we cannot exclude that ADC pathology might emerge as a transient phenomenon, e.g. during a psychotic episode [6], and the findings of previous studies might be accounted for by sample selection (e.g. first-episode vs. chronic samples), our findings and the literature review do not yet suggest a consistent pattern of ADC increase or reductions, even when considering methodological differences.

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Conflict of interest The authors declare that they have no conflict of interest.

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