Schizophrenia Research 161 (2015) 113–118

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The extent of diffusion MRI markers of neuroinflammation and white matter deterioration in chronic schizophrenia

Ofer Pasternak [a,b,*], Carl-Fredrik Westin [b], Brian Dahlben [a], Sylvain Bouix [a], Marek Kubicki [a,b]

[a] Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston 02215, MA, USA
[b] Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston 02215, MA, USA

ARTICLE INFO

Article history:
Received 8 April 2014
Received in revised form 10 July 2014
Accepted 14 July 2014
Available online 10 August 2014

Keywords:
Schizophrenia
Neuroinflammation
Free-water
Degeneration
White matter

ABSTRACT

In a previous study we have demonstrated, using a novel diffusion MRI analysis called free-water imaging, that the early stages of schizophrenia are more likely associated with a neuroinflammatory response and less so with a white matter deterioration or a demyelination process. What is not known is how neuroinflammation and white matter deterioration change along the progression of the disorder. In this study we apply the free-water measures on a population of 29 chronic schizophrenia subjects and compare them with 25 matching controls. Our aim was to compare the extent of free-water imaging abnormalities in chronic subjects with the ones previously obtained for subjects at their first psychotic episode. We find that chronic subjects showed a limited extent of abnormal increase in the volume of the extracellular space, suggesting a less extensive neuroinflammatory response relative to patients at the onset of schizophrenia. At the same time, the chronic schizophrenia subjects had greater extent of reduced fractional anisotropy compared to the previous study, suggesting increased white matter deterioration along the progression of the disease. Our findings substantiate the role of neuroinflammation in the earlier stages of the disorder, and the effect of neurodegeneration that is worsening in the chronic phase.

1. Introduction

The development of diffusion MRI, and its most common analysis method, diffusion tensor imaging (DTI) (Basser et al., 1994), have made it possible to study imaging correlates of white matter pathologies in schizophrenia. Many DTI studies have found decreased fractional anisotropy (FA), and some have found increased mean diffusivity (MD) in different populations of schizophrenia subjects (see Fitzsimmons et al. (2013) for a recent review.) Despite non-specificity of the FA and MD measures, the DTI findings are often considered evidence of a white matter pathology that is likely related to demyelination (Kubicki et al., 2007). Myelin related deficiencies were also inferred from histopathological studies (Uranova et al., 2011), and genetics studies (Davis et al., 2003). An alternative interpretation of the DTI results associates the abnormalities with a neuroinflammatory response, further supported by increased cytokine levels, microglial activation measured with PET, genetic association, and upregulation of inflammatory pathways (see Najjar and Pearlman (2014), for a recent review of neuroinflammation related findings in schizophrenia.)

There is a reciprocal causative relation between neuroinflammation and degeneration, with prolonged inflammatory response that can lead to deterioration, and, on the other hand, inflammation that may be triggered by cellular deterioration (Streit, 2006). Distinguishing between neuroinflammation and deterioration is therefore important to understand the etiology of schizophrenia, and to better target potential treatments. Recently, free-water imaging (Pasternak et al., 2009) was proposed as an analysis method of diffusion MRI that can differentiate the contribution of water molecules diffusing freely in the extracellular space from the contribution of water molecules that diffuse close to tissue membranes. Therefore free-water imaging can help to differentiate between neuroinflammation that is expected to affect the water content in the extracellular space, and white matter deterioration that is expected to affect the tissue itself.

In our previous free-water imaging study, patients diagnosed with schizophrenia were scanned following their first psychotic episode (FE) (Pasternak et al., 2012). It was found that a regular DTI analysis comparing the FE group with matched controls shows a widespread global decrease in FA and overlapping increase in MD. However, applying the free-water imaging analysis revealed that the majority of differences between these groups could be explained as an increase in the extracellular space, and that anisotropy differences in the tissue were only limited to focal areas in the frontal lobe. This disambiguation of the source of differences between the groups led to a conclusion that the early stages of schizophrenia are more likely associated with a

* Corresponding author at: Neuroscience Image Computing, Brigham and Women's Hospital, Harvard Medical School, 1249 Boylston Street, Boston, MA 02215, USA. Tel.: +1 617 525 6162; fax: +1 617 525 6150.
E-mail address: ofer@bwh.harvard.edu (O. Pasternak).

http://dx.doi.org/10.1016/j.schres.2014.07.031
0920-9964/

neuroinflammatory response and less so with a white matter deterioration or a demyelination process.

What is not known is how neuroinflammation and white matter deterioration change along the progression of the disorder. If schizophrenia has a neurodegenerative component, an increased extent of deterioration is expected as the disease progresses. Furthermore, it is not known whether neuroinflammation also plays a role in the chronic stages of schizophrenia. To address these questions, in this study we apply the free-water imaging method on a cohort of chronic schizophrenia (CHR) patients, and compare the extents of deterioration and neuroinflammation with the ones previously obtained for FE patients.

2. Methods

2.1. Subjects

The subjects were 29 patients diagnosed with CHR and 25 controls matched for age, gender, handedness, PSES and premorbid IQ. Patients with CHR were recruited from in-patient, day treatment, out-patient, and foster care programs. DSM-IV diagnoses were based on SCID-P interviews, and information from patient medical records. The CHR subjects were included if they were at least 1 year following diagnosis, however the average duration of illness for this cohort was 15 years (see Table 1). The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) were used to evaluate positive and negative symptoms in schizophrenia (Andreasen, 1983, 1984). The severity of clinical symptoms was also assessed using the positive and negative symptom scale (PANSS) (Kay et al., 1987). In our cohort there was an average score of 10.8 for SANS, 10.2 for SAPS and 22.9 for positive PANSS, 21.7 for negative PANSS and 42.4 for general PANSS. Comparison subjects (group-matched to patients on age, sex, handedness (Edinburgh Handedness Inventory), and parental social economic-status (PSES)) were recruited through advertisements in local newspapers, and tested with SCID-NP interviews. All subjects were included in the study if they met the following criteria: ages between 18 and 55, no history of neurological illness, no alcohol or drug dependence in the last 5 years and no abuse in the past year, right handedness and an ability and desire to cooperate with the procedures. Normal comparison subjects were also screened to exclude first-degree relatives with an Axis I disorder. For demographic details of both patients and controls see Table 1. The study was approved by the local IRB committees. All subjects signed informed consent forms prior to study participation.

2.2. MRI acquisition

All subjects were scanned on a single 3 Tesla General Electric Signa system (GE Medical Systems). This cohort was scanned using the same scanner and protocol as we previously used to scan the FE patients (Pasternak et al., 2012). However, the scans of the current cohort were acquired following a software upgrade, which may have slightly shifted the measurement. Therefore, in this paper we refrain from quantitatively comparing the results previously obtained for the FE subjects with those reported here for the CHR subjects, and instead compare the spatial extent of findings across studies. The complete MRI acquisition is reported in a previous publication (Pasternak et al., 2012). In short, the acquisition included a high-resolution $1.7 \times 1.7 \times 1.7$ mm^3 diffusion MRI sequence, with 51 gradient directions with $b = 900$ s/mm^2, and eight additional $b = 0$ images, in addition to several other anatomical acquisitions.

Table 1
Clinical and experimental parameters.

	Controls		Schizophrenia		
n	25		29		
Female	5		4		
Male	20		25		
CPZ (mg/day)			451 ± 273		
Duration of illness (months)			15 ± 10.5		
IQ	98.92	10.12	101.1	14.7	$p = 0.64$
PSES	2.79	1.38	2.81	0.94	$p = 0.96$
Age (years)	43.68 ± 7.62		46.59 ± 9.504		$p = 0.30$
Education (years)	14.35 ± 1.843		13.75 ± 2.51		$p = 0.16$
Motion (mm)	0.777 ± 0.13		0.786 ± 0.184		$p = 0.84$

CPZ = chlorpromazine equivalent daily dosage; PSES = parental social economic status.

2.3. Free-water imaging

The analysis pipeline replicated the analysis reported in (Pasternak et al., 2012), including motion and eddy current artifact corrections and masking of the diffusion MRI. The free-water imaging maps were obtained by fitting the aligned diffusion MRI data with the free-water model (Pasternak et al., 2009). The model includes two compartments, a free-water compartment and a tissue compartment. The free-water compartment accounts for water molecules that diffuse freely (only likely to be found in the extracellular space), and is described by a single parameter, which is the fractional volume of free-water (FW). The second compartment accounts for water molecules that are in proximity to tissue membranes, which is also the signal that is left following the elimination of freely diffusing water molecules. The tissue compartment is modeled using a diffusion tensor and the tensors are converted to scalar measures by calculating their eigenvalue decomposition. The free-water model can be estimated from a conventional diffusion MRI acquisition, in which case additional mathematical restrictions of continuity are enforced to allow the estimation of the two compartments. The model, as well as the continuity restriction, forms a cost function, and the fitting is done using an iterative process that simultaneously minimizes this function for all of the free parameters, namely the FW parameter and the diffusion tensor representing the tissue compartment. As a result, voxel-wise maps of FA corrected for free-water (FA_T) are obtained, in addition to the voxel-wise FW map. This FA_T parameter is equivalent to the regular FA parameter, yet since the signal from the extracellular space is attenuated, FA_T is more sensitive and specific to geometrical changes that occur in the tissue (Metzler-Baddeley et al., 2012).

2.4. Statistical analysis

To compare between groups we first applied the tract based spatial statistics (TBSS) method (Smith et al., 2006), which uses FA images from all subjects to coregister onto a common space (MNI), and to generate a common white matter skeleton. The different scalar measures (FW and FA_T) were then projected onto the skeleton. Group comparisons were carried using a permutation-based test (randomize, FSL), with a threshold free cluster enhancement, fully accounting for family-wise errors (Smith and Nichols, 2009). The permutation tests included age, gender and motion as covariates. The resulted voxel-wise significance maps were visualized using the FSL software package in 2D (TBSS-fill and FSL view).

Further analysis was performed in selected regions of interest (ROI), which were defined on the white matter skeleton. Diffusivity values were averaged across all voxels in the ROI. In addition, the correlation coefficients of the average values and the total SANS or SAPS scores were calculated using Pearson correlation. In a secondary analysis we looked at each SANS or SAPS score separately, and compared the averaged diffusivity values between symptomatic (score > 0) and non-symptomatic (score = 0) patients using a t-test.

3. Results

Comparing the FW measure between the schizophrenia patients and controls showed localized increased FW (Fig. 1). Voxels with