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MTR abnormalities in subjects at ultra-high risk for schizophrenia and first-episode schizophrenic patients compared to healthy controls

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ABSTRACT

Background: Neuroimaging studies have suggested gray (GM) and white matter (WM) abnormalities in early stages of schizophrenia. We aimed at evaluating subtle parenchymal alterations in individuals at ultra-high risk (UHR) for transition into psychosis and first-episode schizophrenic (FES) patients by measuring the magnetization transfer ratio (MTR).

Methods and material

In a cross-sectional study magnetization transfer images and high-resolution volumetric T1-weighted images were acquired in 70 age- and gender-matched subjects (25 UHR subjects, 16 FES patients and 29 controls) in a 1.5 Tesla scanner. Following normalization of MTR-maps the intensity histograms were analyzed by performing a Kruskal–Wallis-test.

Results: Gray matter MTR decreases were depicted in UHR subjects solely, involving the cingulate gyrus and precentral cortex. WM MTR alterations were more pronounced in FES than in UHR patients and exclusively affected the frontal lobe bilaterally. In addition, UHR subjects showed bilateral MTR decreases at the stria terminalis though statistically significant only on the left side ($p = 0.018$.)

Conclusion: Our results indicate GM affection earlier on during disease progression as well as cumulative WM affection within frontal lobes during transition from UHR to FES. MTR reductions at the stria terminalis of UHR patients points to the involvement of the extended amygdala in the prodromal disease stage.

1. Introduction

Evidence of gray (GM) as well as white matter (WM) changes in patients suffering from schizophrenia have been shown in various studies by using magnetic resonance imaging (MRI) techniques (Hirayasu, 2007).

MRI has also been applied to early stages such as first-episode schizophrenic (FES) patients and those at high risk for disease progression to schizophrenia (ultra-high risk, UHR); in first-episode patients MRI revealed brain volume loss as compared to healthy subjects, in UHR patients gray and white matter abnormalities have been reported in the literature (Steen et al., 2006; Witthaus et al., 2008). Apart from voxel-based morphometry (VBM) studies advanced MRI techniques such as spectroscopy, diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI) have been applied in FES and UHR studies (Price et al., 2006; Wood et al., 2003a, 2008a; Gasparotti et al., 2009). By using MTI Price et al. (2006) could show frontal and temporal abnormalities, suggesting that neuroaxonal and myelin changes were more extensive than those detected with conventional MRI. MTI data with respect to FES and UHR patients are still limited and indicative of magnetization transfer ratio (MTR) changes in regions known for their involvement in schizophrenia without volume loss (Bagary et al., 2003). Thus MTI showed the potential of detecting structural changes in early schizophrenia with a higher sensitivity than VBM-based MRI analysis. Corresponding studies for UHR patients were not available.

To the best of the author's knowledge, this is the first study investigating FES as well UHR patients by MTI.

2. Methods and materials

2.1. Participants

Altogether 70 subjects were included in our study, of which age- and gender-matched subjects belonged to either the UHR group ($n = 25$, 8 women. 17 men, mean age 25.2 ± 4.5 years), the FES group ($n = 16$,

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4 women, 12 men, mean age 25.8 ± 5.8 years) or the control group (n = 29, 12 women, 17 men, mean age 25.7 ± 5.2 years). Table 1 summarizes the demographic and clinical parameters.

The UHR subjects were recruited by the Early Recognition and Intervention Centre (ERIC), Department of Psychiatry and Psychotherapy of the Charité Berlin as part of the Prospective European Prediction of Psychosis Study (EPOS) (Ruhrmann et al., 2010); they were diagnosed according to the Structured Interview for Prodromal Symptoms (SIPS) (McGlashan et al., 2001). The recruitment criterion was at least one attenuated positive symptom with a severity level of at least "three". First-episode schizophrenic patients were in-patients or had frequent contact to the outpatient clinic; they were first diagnosed with schizophrenia according to the fourth version of the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-IV) of the American Psychiatric Association and had at least one of the following symptoms: delusions, hallucinations or formal thought disorder (PANSS-items P1–P3, P5–P6 ≥ 4).

Before being included in the study, all subjects underwent medical examination and blood and urine tests to exclude physical health problems. The healthy control subjects were screened with the m.i.n.i. SCID for mental diseases in their own or family history (Sheehan et al., 1998). Subjects with a history of neurological or severe somatic illness, head injury, alcohol dependence or substance abuse were excluded. Inclusion and exclusion criteria for study participants have been previously described in detail (Witthaus et al., 2008).

We determined handedness by the Edinburgh inventory (Oldfield, 1971) and estimated premorbid verbal IQ using MWT-B (Lehrl, 1978).

For assessing psychopathological signs and symptoms, the PANSS and SIPS were used (Kay et al., 1987). The study was approved by the local ethics committee and carried out in accordance with the Declaration of Helsinki. All subjects gave written informed consent after the study design and procedures had been fully explained to them. A neuroradiologist reviewed all MRI brain scans; no gross abnormalities were observed.

2.2. MRI scanning protocol and data processing

MRI was performed on a 1.5-Tesla Siemens MAGNETOM Symphony Scanner (Siemens, Erlangen, Germany). A 3D structural MRI was acquired on each subject using a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence (TR 2280 ms, TE 3.93 ms, TI 1100 ms, flip angle 15°, yielding 160 sagittal slices with a thickness of 1.0 mm).

2.3. Magnetization transfer imaging

MTI measurements allowed for determining the average transfer ratio within the brain parenchyma. An off-resonance radiofrequency pulse with 1.5 kHz distance to the Larmor frequency of hydrogen, 16.4 ms duration, 850° angle and 768 Hz bandwidth was chosen. Measurements were programmed in a way that a gradient echo sequence without off-resonance pulses was immediately followed by the one using off-resonance pulses.

Table 1
Demographic and clinical data.

	UHR (n = 25)	FES (n = 16)	Controls (n = 30)	Statistics
Age, years	25.2 ± 4.5	25.8 ± 5.8	25.7 ± 5.2	$F_{(2,69)} = 0.939$, n.s.
Male/female	17/8	12/4	17/12	$\chi^2 = 1.318$, n.s.
Handedness: right-left-mixed or unknown	22/2/1	10/3/3	23/5/1	$\chi^2 = 5.821$, n.s.
Antipsychotic medication: yes/no	9/16	4/12	0/29	$\chi^2 = 12.073$, $p = 0.002$
Duration of previous antipsychotic medication	<3 weeks	<10 days		
PANSS positive	12.3 ± 3.5	17.9 ± 5.0		$t = 4.170$, $p < 0.001$
PANSS negative	13.7 ± 5.3	18.3 ± 5.8		$t = 2.645$, $p < 0.02$

2.4. MTR maps

The MTR-maps have been calculated by using the following equation per every voxel:$MTR = (T_0 - T_{mt})/T_0$. T_0 represents the intensity value of the voxel in the non-saturated sequence and T_{mt} the value of the corresponding voxel in the sequence saturated by the MT-pulse. The normalization of the MTR-maps was performed by means of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). All subjects were normalized by using an 'ICBM space template—European brains' (MNI 152) provided with SPM8.

2.5. Regions of interest (ROI)

In order to minimize co-registration mismatches by the use of partial brain images and to preserve as much of the original grayscale information as possible, a minimal smoothing kernel was chosen in the size of 2 × 2 × 2 mm and normalization was performed using SPM8's T1 template. Following post-processing the image size was 180 × 216 × 180 mm with 91 × 109 × 91 of isotropic voxels of size 2 × 2 × 2 mm. The analysis was conducted with MATLAB® (The MathWorks Inc., Natick, Massachusetts, USA). The program script written for MATLAB® iteratively performs a Kruskal–Wallis-test on the intensity histograms of two test groups and writes the result in the output volume (91 × 109 × 91). It uses 3D-kernel with the constant size of 5 × 5 × 5 voxels, which moves incrementally along all three spatial axes and reads the intensity values from all subjects. At every step the two intensity histograms are generated for the spatial position of the kernel and for the subject group, respectively. If $p < 0.01$ applies at some step, the values of all voxels in the corresponding region of the output volume (91 × 109 × 91) would be increased by 1. Since the kernel always occupies 125 voxels, the possible intensity range for the output volume is 0–125, where 0 means no significant test and 125 that all tests were significant. ROIs were generated by filtering the resulting voxels with the intensity value below 63 (<50.4%). Only those subjects with a co-registration error within a single slice (± 1 mm) as compared to all subjects were included in further testing. We found 10 subjects eligible in each group. We tested: FES against Control, UHR against Control and FES against UHR.

2.6. Data and statistical analysis

Group differences in demographic and clinical parameters were assessed using ANOVA and Chi-squared test (Table 1). MTR group differences for a single ROI were evaluated using the Kruskal–Wallis-test (Tables 2 and 3).

The ratios of summed intensity values were calculated from the group histograms by using the following equation:

$$\mathbf{r} = \left(\sum \mathrm{Count}_{(\mathrm{Intensity})} \times \mathrm{Intensity}\right)_{\mathrm{FES\ or\ UHR}} \div \left(\sum \mathrm{Count}_{(\mathrm{Intensity})} \times \mathrm{Intensity}\right)_{\mathrm{Control}}$$

The ROI volume was calculated by multiplying the number of voxels from a single ROI volume mask with the single voxel size (2 × 2 × 2 mm).

3. Results

Nine UHR subjects were treated with either risperidone or olanzapine in low dosages and only for a few weeks (less than three weeks). Four FES patients received typical or atypical antipsychotics in clinical dosages,