Neuro-anatomical correlates of neuropsychological and psychopathological domains in first episode schizophrenia: a multimodal analysis.

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Purpose

In the past years several researchers have investigated the possible associations between brain structural abnormalities and schizophrenia, even at the early phases of the disease [1,2].

Structural abnormalities of grey matter (GM) found in first-episode schizophrenia (FES) are supposed to be unbiased by secondary processes such as duration of illness, long-term treatment and different outcome variants, and therefore ideally reflecting only the primary pathological changes.

If the whole pattern of GM abnormalities reflects an aberrant neuronal network, a concomitant alteration of white matter (WM) tissue might also be observed.

Interestingly, recent studies suggested that WM abnormalities were present since the onset of the disease and that WM abnormalities of the temporal regions may account for memory functioning impairment in the early course of schizophrenia, while deficits of executive and motor functioning might depend on WM disarray of the major tracts connecting fronto-temporal cortices [3].

Unfortunately, GM volume and WM integrity have not been explored together in correlation with neuropsychological performances, so far.

Over the years, functional neuroimaging techniques have provided a great body of evidence about cognitive functions, but unfortunately the tasks used for brain activation often do not explore the same functions and are generally less standardized than neuropsychological tests.

Accordingly, pure structural approaches such as voxel based morphometry (VBM) and Tract-Based Spatial Statistics (TBSS), for GM and WM investigation respectively, might present less methodological caveats than functional neuroimaging.

The purpose of our study was therefore to use VBM and TBSS to investigate GM volume and WM integrity in FES, correlating GM and WM structural changes with symptoms and neurocognitive scores.
Methods and Materials

Subjects

All consecutive patients referring to the acute psychiatric care and to the outpatient psychiatric service of Sant'Andrea Hospital of Rome between October 2010 and June 2011 were enrolled if fulfilling the following requirements: i) age between 18 and 30 ii) presenting their first episode of non affective psychosis according to DSM-IV-TR criteria for schizophrenia, schizophreniform disorder or brief psychotic disorder iii) receiving adequate antipsychotic treatment for less than two weeks. Diagnosis was made using the Structured Clinical Interview for DSM-IV (SCID-I) by two senior psychiatrists in consensus. Duration of untreated psychosis (DUP) was defined as the time from the first continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic treatment. The first identifiable positive symptom was determined using data gathered from multiple sources, including medical records and direct interviews with both patient and family members.

Mayor exclusion criteria were i) current or past diagnosis of autistic disorder or other pervasive developmental disorder, ii) history of severe head injury, iii) severe medical conditions or major neurological disorders, including mental retardation and dementia, that could prevent neuropsychological task performance or that could produce psychotic symptoms, and iii) any current or past drug abuse.

Ten healthy volunteers were recruited as controls by word of mouth in the same catchment area.

None had prior history of psychiatric disease, mental retardation, neurological or general medical illnesses, including substance dependence, as determined by using an abbreviated version of the Comprehensive Assessment of Symptoms and History (CASH). Controls were age-, gender-,handedness-, and education-matched with patients. The absence of psychosis in first-degree relatives was confirmed by clinical records and family interview. Written informed consent was obtained from all participants after providing complete description and explanation of the study.

Ethical approval was obtained. The study followed the Declaration of Helsinki and Good Clinical Practice guidelines.

Psychopathological assessment

Patients' clinical symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) by two specialists who were unaware of the purpose of the study. Handedness was assessed by the Edinburgh Inventory. Median time from admission to full psychopathological assessment was 14 days (range: 7-20 days).
**Neuropsychological assessment**

Neuropsychological assessment was carried-out according to the "Measurement and Treatment Research to improve Cognition in Schizophrenia" (MATRICS), including the exploration of seven domains, i.e., speed of processing, sustained attention/vigilance, working memory, verbal memory, visual memory, reasoning and problem-solving, and social cognition. Median time from admission to neuropsychological assessment was four weeks (range: 17-35 days), which was deemed to be adequate for the acute state to be stabilized.

**MRI acquisition and image processing**

Median time elapsed from admission to MRI acquisition was 4 ± 1.5 days. A single MRI scan of all subjects was acquired on a 1.5 Tesla MR scanner. The imaging protocol comprised 3D T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE), FLAIR sequence and Diffusion tensor imaging (DTI) data acquired using a twelve-direction sequence.

**Grey matter analysis:**

VBM was performed by using the Statistical Parametric Mapping package (SPM8) and the DARTEL registration method [4].

Brain segmentation was performed using Statistical Parametric Mapping 8 running under MATLAB R2011a. The segmented images were imported to DARTEL for warping procedure, and then iteratively aligned to the average template. During DARTEL warping, the segmented images were modulated with Jacobian determinates to preserve volume changes.

Normalized modulated GM was finally smoothed with an 8 mm full width at half maximum Gaussian kernel. GM, WM and cerebrospinal fluid volumes were calculated using SPM 8.

**White matter analysis:**

DTIs were corrected for the effects of head movements and eddy currents using the eddy-correct function. The registered images (b0 and the twelve directions files) were skull-stripped using the FSL Brain Extraction Tool. Fractional anisotropy (FA) maps were calculated using DTIFit which fits a diffusion tensor model at each voxel.

In order to perform a voxelwise analyses of FA images we used TBSS v.1.2.

All FA images were coregistered to the Montreal Neurological Institute-152 space FA template using FNIRT and were fed into the FA skeletonization program to create the mean FA skeleton [5].
**Statistical analysis**

Sociodemographic and neuropsychological statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS vers. 16).

To analyse data from MRI scans, a general linear model through pre-processed images was set-up.

Two-sample \( t \)-test was applied to provide voxel-wise group comparisons of GM volumes with age, gender, years of education and total intracranial volume (TIV) as covariates. TIV was calculated as the sum of GM, WM and cerebrospinal fluid (CSF) volumes. GM probability maps were filtered at uncorrected \( p < 0.005 \) and a minimum cluster size of 100 voxels. A Family-wise error (FWE) correction was subsequently applied. The anatomic localization of significant clusters of GM analysis was detected using the tool FSL-view of FSL software and Talairach Demon Labels atlas.

Comparisons of FA between groups were tested by a two-sample \( t \) test adjusted for patient's age and gender. The number of permutations was set at 500. Voxelwise FA statistical analysis was performed by using a permutation based inference tool for non parametric statistical thresholding ("randomize" program, part of FSL), at first using a statistical threshold of \( p<0.005 \) and then using a threshold of \( p<0.05 \) corrected for multiple comparisons by implementing threshold-free cluster enhancement (TFCE). The anatomic location of significant clusters was detected using the Johns Hopkins University WM tractography atlas, part of FSL view tool.

For psychopathological correlative-analyses GM volume and WM FA were correlated separately with PANSS negative and disorganized factors, respectively. These symptoms have previously been related to brain volume and may represent a more stable psychopathological subset [6]. Other domains were excluded from this analysis because exploring symptoms which are thought to be unstable, statedependent and difficult to correlate with brain structure [6].

Differences of neuropsychological measures between patients and controls were analyzed by using the Mann-Whitney U-test. For neuropsychological correlative-analyses, only those neuropsychological measures which retained their statistical significance in differentiating between patients and controls after Bonferroni correction were correlated to GM volume and WM FA respectively. As previously described, age, gender years of education and TIV were used as covariates and the same statistical threshold values were applied.
Results

**Sociodemographic characteristics and clinical variables in patients and controls**

Twenty-five patients were enrolled. Despite our efforts to motivate them, 5 patients decided to quit the study because feeling not comfortable to undergo the MR scan; 3 patients denied consent just prior to MR scanning, while other 2 patients refused to complete the ongoing scan. Another patient, who was able to complete all sequences but obtained images of poor quality because of movement artefacts, was excluded from the final analysis. Therefore, a final set of 19 patients, with a high quality MRI scan, was analyzed.

Sociodemographic characteristics and main psychopathological domains of PANSS are shown in Table 1 (see Table1). Patients did not differ from controls for general features (all \( p > 0.3 \)).

**Neuropsychological measures in patients and controls**

Complete results of neuropsychological tests are shown in Table 2 (see Table2).

The following neuropsychological measures retained statistical significance after Bonferroni correction (all \( p < 0.005 \)) and entered the subsequent correlative analyses: (1) Social cognition (FEIT); (2) Speed of processing (Stroop W); (3) Visual Memory (ROCF).

**Grey matter volume comparisons between patients and controls**

Relative to controls, patients showed significantly decreased GM volume in the superior, middle, inferior and fusiform gyrus of the left temporal lobe [Brodmann area 37] at uncorrected cluster level (\( p = 0.003 \)). As shown by Table 3, a trend towards significance was found for the decrease in right cerebellum and right cuneus [Brodmann area 17] volumes (\( p < 0.03 \) and \( p < 0.09 \), respectively) (see Table 3). No significant increases in GM volume were found in patients compared to healthy controls. Figure 1 depicts regions of GM volume reduction in FES (see fig.1).

**White matter structural abnormalities in patients compared to controls:**

WM analysis revealed significant decreased FA values in patients compared to controls in all major WM tracts, including thalamic radiations, cortico-cortical associations tracts (uncinate, inferior and superior longitudinal fasciculus, inferior fronto-occipital fasciculus), interhemispheric tract (splenium of the corpus callosum) and cortico-spinal tracts (uncorrected \( p < 0.005 \)) (see fig.2)
**Correlation between psychopathological features and grey matter**

A significant correlation between PANSS disorganized/cognitive factor score and GM decrease was found in the left cerebellum. Table 4 shows the complete results of the statistical correlation between PANSS scores and morphometric GM analysis (see Table 4).

**Correlation between psychopathological features and white matter**

A significant inverse correlation between PANSS disorganized/cognitive factor score and FA was found in the left cerebellum, the inferior fronto-occipital fasciculus bilaterally, the inferior longitudinal fasciculus bilaterally and part of the commissural fibers (body and splenium of the corpus callosum) (corrected \(p<0.05\)). Furthermore, a significant inverse correlation between PANSS negative factor and FA was found in the inferior fronto-occipital fasciculus bilaterally, superior longitudinal fasciculus bilaterally and splenium of the corpus callosum (corrected \(p<0.05\)).

**Correlation between neuropsychological performances and grey matter**

In patients, FEIT score (i.e. social cognition) significantly correlated with a GM decrease in the right temporal-occipital cortex [Brodmann's area 37]. A correlation was found between i) speed of processing and decreased left cerebellar GM volume and ii) visual memory and GM decrease in right cerebellum, without reaching statistical significance (see Table 4).

**Correlation between neuropsychological performances and white matter**

Patients displayed a significant correlation between FEIT score and WM disarray of the superior and middle temporal gyrus bilaterally, anterior thalamic radiation, superior longitudinal fasciculi, genu and body of the corpus callosum (corrected \(p<0.05\)).

Speed of processing and visual memory showed a similar pattern of associated WM disarray: both correlated with FA of frontal (i.e. parts of the anterior thalamic radiation, and inferior fronto-occipital fasciculus, bilaterally) and left temporal WM areas (i.e. superior longitudinal fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus) (uncorrected \(p<0.001\)).
Fig. 1: Brain regions showing GM decrease in FES patients compared to controls (red).

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Fig. 2: WM disarray in FES compared to controls. WM analysis revealed a diffuse reduction of FA in patients compared to controls. Regions of significant FA reduction are shown in red on axial, coronal and sagittal planes projected into the mean FA skeleton (green). Z= coordinates of MNI.

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Table 1: Socio-demographic characteristics of patients and controls. Abbreviations: FES: First Episode Schizophrenia; HC: Healthy Controls; DUP: Duration of Untreated Psychosis; Standard deviation from the mean value is reported in brackets.

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Table 2: Neuropsychological domain in FES and HC. Abbreviations : FES : First Episode Schizophrenia ; HC : Healthy controls ; TM A: Trail Making A, Stroop W: Stroop Word test, WCST NPE: Wisconsin Card Sorting Test nonperseverative errors, TM B-A: Trail Making B-A, ROCF: Rey-Osterrieth Complex Figure, WCST CC : Wisconsin Card Sorting Test number of completed categories, RSPM: Raven Standard Progressive Matrices, Stroop CW, Stroop Color Word test, FAR : facial affect recognition. *p < 0.05 ; **p< 0.005 (Mann-Whitney U)

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Table 3: GM volume reduction in FES patients compared to controls. The table displays only regions with at least a trend toward statistical significance at uncorrected cluster level. Abbreviations: MNI (Montreal Neurological Institute) coordinates. Also showed number of significant voxels (K-value) in the area, p-value, and Z-value.

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Table 4: Correlations between psychopathological/neuropsychological measures and grey matter volume (GMV) in FES. Abbreviations: GMV: Grey Matter Volume; FES: First Episode Schizophrenia; ROCF: Rey-Osterrieth Complex Figure

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Conclusion

In recent years, schizophrenia has been proposed as a neuro-developmentally derived "misconnection syndrome" involving connections between cortical regions and the cerebellum mediated through the thalamus (the cortico-cerebellar-thalamic-cortical circuit, CCTCC) [7].

Abnormal CCTCC leads to misconnection in many aspects of mental activity, or to "cognitive dysmetria", which is substantially a pattern of disorganization. Following this theory, significant correlations between symptoms, cognitive performances and cerebral anatomy might be detected in schizophrenia. Inherently with the concept of "neuro-development", it appears likely to find such correlations since the onset of the disease.

In the present study, whole-brain, rater-independent VBM was carried out to investigate GM and WM volume abnormalities at the onset of schizophrenia (FES), addressing possible neuroanatomical underpinnings of symptoms and cognitive impairment.

Firstly, our results suggest the presence of a reduction in left temporal GM volume in patients as compared to controls, which has been advocated as a trait feature of chronic schizophrenia. Our findings are consistent with those of some authors [6], while others showed GM reduction in different regions [1]. Factors which may underlie the differing patterns of morphological changes in FES are numerous, rendering difficult any comparison with previous studies. Since sociodemographic and clinical characteristics of our series were comparable with the previous investigations applying VBM in FES, differences between other reports may be due to different definition of first-episode, duration of illness before assessment and type of medication. We hypothesized that the influence of antipsychotic treatment in GM volume of our population was unlikely, as we had only patients treated for less than 14 days. Variations in VBM methodology, such as normalization parameters may affect the sensitivity of the study to detect changes in some brain regions, particularly in medio-temporal regions; differences of image smoothing may affect the number of areas of volume reduction detected [1]. The SPM8 model and the DARTEL registration method used in our study allows for the identification of structural changes with a more accurate inter-subject alignment, obtaining a correct realignment of small inner structure [4].

The second finding of our study was a disarray of all major WM tracts in patients compared to controls. Although obtained in a small sample, this finding suggests the presence of WM disarray since the onset of the disease, sustaining that neurological aberrations lead to intra and interhemispheric deregulated connectivity, which may explain the global nature and heterogeneity of cognitive deficits in schizophrenia [2].

As far as imaging correlates are concerned, to the best of our knowledge this is the first study examining the relationship between GM volume, WM integrity and both psychopathological and neuropsychological measures in FES.
Firstly, the disorganized/cognitive PANSS factor was associated with decrease of GM volume and FA disarray in the left cerebellum. Cerebellum is involved in basic neurocognitive functions such as timing and associative learning and plays a significant role in cognition. It is activated in a variety of mental activities including facial recognition, emotion attribution, directed attention and memory. To the best of our knowledge, this is the first study identifying, in the early course of schizophrenia, the disorganised psychopathological pattern related to volume deficits and microstructural disarray in that region.

Secondly, negative symptoms displayed a significant inverse correlation with FA of the major WM cortico-cortical association tracts. This is consistent with previous studies and may be explained by the "functional disconnection" hypothesis, according to which a disconnection between frontotemporal WM areas might be related to negative symptoms of schizophrenia [3].

Unfortunately, we failed to detect a correlation between negative symptoms and cortical GM volume.

Correlative neuropsychological analysis showed additional interesting results. Social cognition impairment was related to a GM decrease in right temporo-occipital cortex and to a concurrent WM disarray of superior and middle temporal gyrus bilaterally, anterior thalamic radiation, and superior longitudinal fasciculus. As supported by recent literature, impaired social cognition is a core feature of schizophrenia. The correlation found with GM volume is in line with a previous study in first episode psychosis [8]. On the other hand, WM abnormalities could be partially included in the revised face-perception circuitry, composed of a core system (temporooccipital regions) mediating the visual analysis of faces, and of an extended pathway (frontal-limbic system) deriving meaning from face perception [9].

Results at uncorrected cluster levels are also discussed below; low statistical power may represent a possible caveat, but is perhaps allowed by the preliminary nature of our study.

In summary, this is an original exploratory study of anatomical underpinnings of neuropsychopathology in FES. While the small number of patients is of course a weakness of the study, one strength is represented by the selection of patients. All patients included had an untreated psychosis for less than 12 months before admission and all had diagnostic confirmation of schizophrenia six months after study entry. This supports the accuracy of our diagnoses of FEP.

Moreover, a possible confounding factor in the evaluation of cognitive function, such as the history of prior drug abuse, has been excluded in all our patients. Of note, controls were matched for age, gender, education, which could be confounding factors when inferring cognitive function from brain structure.
Consistently with a neurodevelopmentally derived "misconnection syndrome" [10], our results show how the structural development of key brain regions is related to neuro-psychopathological dysfunction even at the very early stages of schizophrenia. Overall, confirmatory longitudinal studies are needed.
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