Brain morphometry correlates of pharmacoresistancy in schizophrenia

M. Quarantelli[1], O. Palladino[2], A. Prinster[1,3], V. Schiavone[2], B. Carotenuto[4], A. Brunetti[4], G. Ventrella[2], A. Marsili[1], A. De Bartolomeis[2], and M. Salvatore[4]
[1]Biostructure and Bioimaging Institute, National Research Council, Naples, Italy, [2]Institute of Psychiatry, University "Federico II", Naples, Italy, [3] "S.D.N." Foundation, Naples, Italy, [4]Department of Biomorphological and Functional Sciences, University "Federico II", Naples, Italy

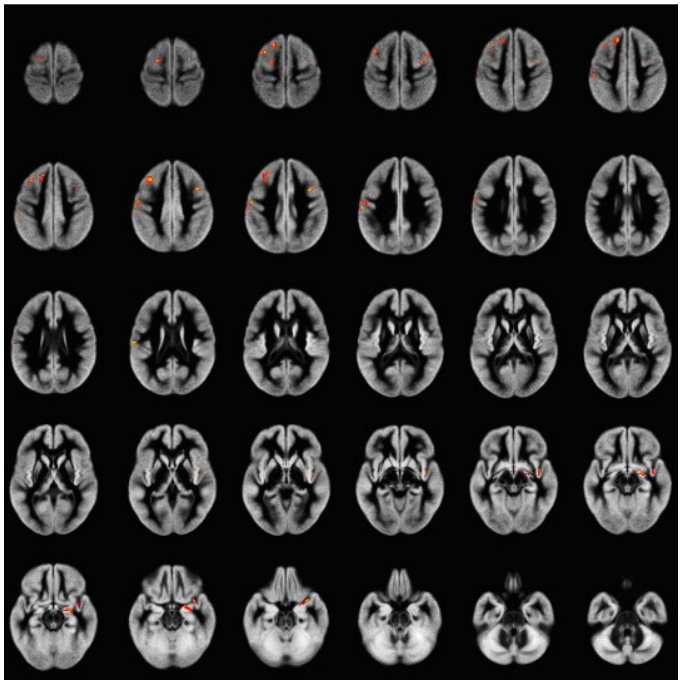
***Introduction*:** Although several studies have demonstrated the presence of brain structural alterations in schizophrenia [Am J Psychiatry 2005;162:2233], to the best of our knowledge only one study, using a Region of Interest approach, has assessed structural correlates of treatment-resistant schizophrenia [Prog Neuropsychopharmacol Biol Psychiatry 2008;32:257], suggesting lower GM volume in frontal and occipital regions in Non Responder (NR-SC) schizophrenia patients compared to Responders (R-SC).

We designed a pilot study to explore, by mean of voxel-based analysis of segmented MR studies, structural cerebral differences between R-SC and NR-SC.

Subjects: 19 NR-SC and 16 R-SC (classified according to Kane et Al. [Arch Gen Psychiatry 1988;45:789] and matched in terms of disease duration and age at onset), and 16 normal volunteers (NV) were enrolled. All subjects were male and right-handed, the three groups were age-matched. All patients were under antipsychotic treatment, the protocol was approved by the ethical committees of participating Institutions and written consent was obtained.

Morphometric analysis: T1-weighted volumes were acquired at 1.5 Tesla (Achieva, Philips Medical Systems, NL) using a magnetization-prepared 3D fast Gradient-Echo sequence (TR/TE/TI 11/2/600ms, voxel size 0.98x0.98x1.2mm, 124 contiguous axial slices), and segmented by the unified segmentation approach [NeuroImage 2005;26:839] implemented in SPM5 (Wellcome Department of Cognitive Neurology, London, UK). GM volumes were normalized to the MNI space, modulated [Neuroimage 2000;11:805], and smoothed (5mm FWHM).

Local differences in gray matter volume between the three groups were assessed using permutation tests [IEEE Trans Med Imaging 1999;18:32] [Hum Brain Mapp 2004;22:193] implemented in the CamBA software (http://www-bmu.psychiatry.cam.ac.uk/software).



Areas of significantly reduced gray matter in non-responder compared to responder schizophrenia patients, superimposed onto the averaged normalized GM volumes. Right side of the brain is at the observer's right.

A preliminary voxel-wise omnibus ANCOVA, including total intracranial volume and age as covariates, was performed to localize relative GM group differences among the three groups, followed by three post-hoc analyses of significant main effects, probing both direct and inverse contrasts.

Probability thresholds for cluster testing, against values obtained by 10 random permutations of the data sets, were set so that the average number of false-positive clusters expected per map was less than one. Significant clusters were localized based on their coordinates in the MNI space [Neuroimage 2002;15:273].

Results: Clusters of significant GM differences among the three groups emerged mainly in bilateral frontal cortices and right insula and medial temporal lobe. Post-hoc analysis disclosed that differences were mainly due to a reduced GM volume of these structures in NR-SC, as compared to both NV and R-SC (see figure).

***Discussion and Conclusion*:** Our results suggest that differences between NV an SC may be mainly driven by NR-SC patients.

Results of this pilot study need to be confirmed in larger patient populations and in longitudinal studies in drug-naïve patients, to assess a potential predictive value of these alterations and/or the relationship between TRS and putative neurodegenerative phenomena which may play a role in SC.