Functional connectivity of altered grey matter regions in Autism Spectrum Disorder: correlations with clinical testing

Letizia Casiraghi[1,2], Fulvia Palesi[2,3], Gloria Castellazzi[2,4], Andrea De Rinaldis[2,4], Carol Di Perri[5], Claudia AM Wheeler-Kingshott[6], and Egidio D'Angelo[1,2]

[1]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, PV, Italy, [2]Brain Connectivity Center, C. Mondino National Neurological Institute, Pavia, PV, Italy, [3]Department of Physics, University of Pavia, Pavia, PV, Italy, [4]Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, PV, Italy, [5]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, PV, Italy, [6]NMR Research Unit, Department of Neuroinflammation, Queen Square MS Centre, UCL Institute of Neurology, London, England, United Kingdom

Target Audience: Clinicians and researchers with an interest in autism spectrum disorder.

Purpose: Autism Spectrum Disorder (ASD) is an early onset disability with a variable developmental trajectory [1]. ASD children present atypical social interaction, communication and repetitive behaviour [2]. Despite the large number of studies reporting the disruption of structural and functional connectivity in ASD, findings are inconsistent and there is a striking lack of research attempting to integrate these kind of analyses [3,4]. By selecting high-functioning ASD children we were able to study possible cerebral correlates of core autistic features avoiding confounds due to below-average intellectual functions. In this study we assessed grey matter (GM) structural alterations and their functional connectivity (FC) in ASD combining Voxel Based Morphometry (VBM) and seed based FC analysis. Furthermore we investigated the relationships between aberrant FC and behavioural scores in ASD.

Methods: We used publicly available data from the Stanford University ABIDE Database [5]. Subjects: 20 children (mean age 9.8±1.5 years) who met criteria for ASD on the Autism Diagnostic Observation Schedule (ADOS) or criteria for autism on the Autism Diagnostic Interview-Revised (ADI-R) and 19 Typically Developing (TD) children (mean age 10.3±1.6 years) underwent MRI examination using a 3T GE Signa scanner (General Electric, Milwaukee, Wisconsin). MRI acquisition: 1) Resting state fMRI GE-EPI with TR=2000ms, TE=30ms, flip angle=80°, FOV=200mm, voxel size=3x3x4.5mm^3, 29 slices for a total of 180 volumes; 2) For anatomical reference, high-resolution 3D coronal T1-weighted (3DT1w) scan with TI=300ms, TR=8.4ms, TE=1.8ms, flip angle=15°, 2 excitations, FOV=220mm, slice thickness=1.5mm, in-plane resolution = 0.9x1.1mm^2 and 132 slices. Structural analysis: VBM analysis was performed on the 3DT1w images of all 39 subjects recruited for the study using SPM8 [6]. Statistical analysis was performed using the general linear model (GLM) framework and the GM map as explicit mask. A statistical threshold of $p<0.001$ was considered significant and an extent threshold of 20 voxels was used to set the false discovery rate (FDR). Seed based fMRI analysis: The peaks of GM clusters (VBM results of increased volume and reduced density in ASD) were used to define the centre of 7 spherical (r=4mm) seeds. Seed based fMRI analysis was carried out using BrainVoyager QX software version 2.8 [7] on a subgroup of 19 ASD and 15 TD. For each participant motion parameters, the average time course in white matter, and the average time course in CSF were used as regressors. Correlation maps for each seed were created using a multiple-regression approach. The random effect ANCOVA was applied to compare group-specific maps. Statistical maps were finally corrected for multiple comparisons using a cluster threshold approach based on Monte Carlo simulation and a statistical threshold of $p<0.01$ was considered significant. Correlations with clinical scores: A standard Pearson correlation analysis ($p<0.05$) was performed between FC values and clinical evaluations (ADI and ADOS subscales) using SPSS.

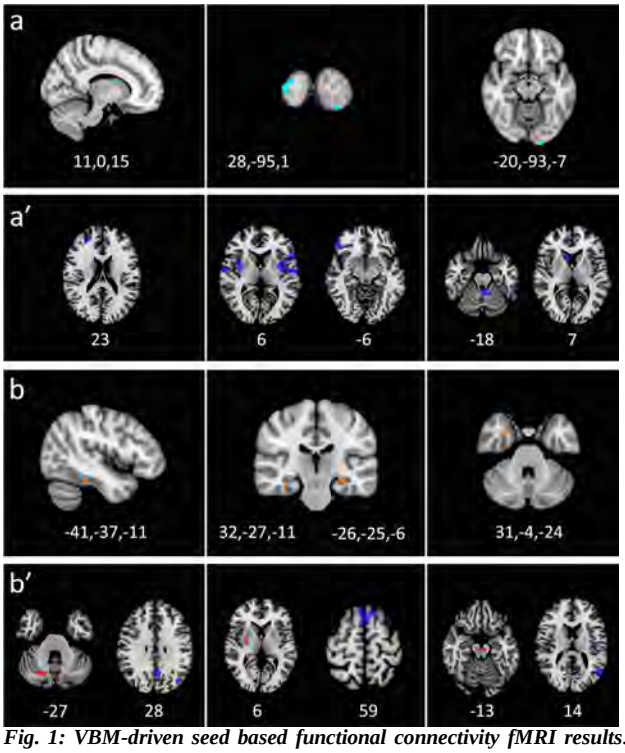

Fig. 1: VBM-driven seed based functional connectivity fMRI results*. x,y,z coordinates are in Talairach space (mm). Z coordinates are reported for each axial slice.* ***a)*** *VBM density reductions (light blue).* ***a')*** *Seed based FC reductions (blue).* ***b)*** *VBM volume increments (orange).* ***b')*** *Seed based FC reductions (blue) and increments (red).*

Results: VBM (figure 1 a and b) revealed significant density reductions in ASD in the occipital lobe (bilateral visual associative areas) and right caudate. Increased GM volume in ASD was observed in temporal and limbic areas such as bilateral parahippocampi, left hippocampus (HC) and inferior temporal gyrus. GM density increments and GM volume reductions didn't survive the cluster threshold correction. Seed based fMRI analysis (figure 1 a' and b') revealed areas of reduced FC in limbic system (bilateral insula and left posterior cingulate cortex), frontal lobe, left inferior occipital lobe, left middle temporal gyrus, right caudate and cerebellum. Increased FC was found in subcortical structures, i.e. putamen and red nuclei, and in right cerebellum linked to left hippocampus, right parahippocampus and left inferior temporal lobe respectively. In ASD, we found correlations between FC of the limbic/subcortical system and social interactions (p=.009), verbal ability (p=.032) and repetitive behaviours (p=.038) and anti-correlations between FC of the hippocampus/frontal system and socio-affective interactions (p=.030), visual/insular link and repetitive behaviours (p=.005) and visual/orbitofrontal link and ADOS (p=.037).

Discussion and conclusions: This work investigates the possible correlates between ASD structural abnormalities and FC changes of related areas with a seed-based analysis. The presence of changes in GM volume, density and FC confirms the complexity of ASD. Correlations between FC and clinical scores indicate that the more extreme the FC value (min/max range values) from seed regions of structural abnormalities the more severe the impairment. Medial and inferior temporal lobe and subcortical structures are classically involved in flexible multidimensional association of sensory stimuli and motivational states with experience and learning [8] while visual associative cortex and insula have a role in the processing of emotional and attentional aspects of visual perception, body representation and sense of agency [9]. Our correlations between FC and social abilities and repetitive behaviours support the idea that temporal and subcortical areas are responsible for the sensory integration and emotional deficits in ASD (i.e. rigid behaviour and aberrant modulation of the limbic system) while anti-correlations between FC and repetitive behaviours suggest that visual associative areas and insula are strongly involved in ASD deficit linked to the integration of visual stimuli and self-awareness information. Novel findings are reduced FC in areas such as the superior frontal lobe, orbitofrontal gyrus and cerebellum, which can suggest that there are also high-level deficits concerning working memory, executive control and decision making. Further studies are warranted to confirm our results and to assess the causal relationship between FC and structural changes in ASD.

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