Coexistence of enhanced and reduced Default Mode Network functional connectivity in Autism Spectrum Disorder

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Target Audience: Clinicians and researchers with an interest in autism spectrum disorder and resting state functional connectivity.

Purpose: Autism Spectrum Disorder (ASD) is a neurodevelopmental disability with early onset and variable developmental trajectory [(1)]. The ASD behavioural phenotype includes persistent impairment in social communication and interaction [(2)]. Several resting state functional Magnetic Resonance Imaging (rs-fMRI) studies have associated ASD with disruptions in brain functional connectivity (FC), such as in cingulate cortex (CC) of the default mode network (DMN) bringing to the "under-connectivity theories" [(3)]. Conversely, Uddin et al. [(4)], using Independent Component Analysis (ICA), have detected enhanced DMN FC in precuneus, posterior CC and left angular gyrus in the DMN of ASD compared to tipically developing (TD) children. They didn't observed reductions. Therefore, a standard pattern of FC alteration in ASD is not defined. In this study we used ICA analysis on ASD and TD subjects in order to test the influence of methodological choices on results and to investigate the differences in FC focusing on the DMN.

Methods: We used publicly available data from *Stanford University ABIDE Database* [(5)]. *Subjects:* 20 children aged 7.9 to 12.9 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 TD children aged 7.7 to 12.4 years underwent MRI examination using a 3T GE Signa scanner (General Electric, Milwaukee, Wisconsin). *MRI acquisition:* 1) Resting state fMRI GE-EPI (TR=2000 ms, TE=30 ms, flip angle=80°, FOV=200mm, voxel size=3x3x4.5 mm^3, 29 slices for a total of 180 volumes, acquisition time=6min); 2) For anatomical reference we used high-resolution 3D coronal T1-weighted (3DT1w) with TI=300 ms, TR=8.4 ms, TE=1.8 ms, flip angle=15°, 2 excitations, FOV=220 mm, acquisition matrix=256x192 (reconstructed to 256x256), slice thickness=1.5 mm, in-plane resolution = 0.9x1.1mm and 132 slices. *fMRI analysis:* For each subject, rs-fMRI images were analysed using the ICA computational method in order to characterise resting state networks (RSNs). ICA analyses (single-subject and group-level ICAs) were carried out using BrainVoyager QX software 2.8 version (Brain Innovation, Maastricht, the Netherlands) and the relative plug-in extensions (fast ICA algorithm and self-organizing group-level ICA algorithm) [(6, 7)]. The random effect ANCOVA (RFX ANCOVA), as implemented in BrainVoyager QX, was then applied in order to compare group-specific maps for each independent spatial component. Statistical maps were multiple comparisons corrected using the cluster treshold estimator plugin available in BrainVoyager. A statistical treshold of $p < 0.05$ was considered significant.

Results: ICA analysis resulted in 30 independent components (ICs), 6 of which were recognized as RSNs: DMN, Cerebellar Network (CBLN), Dorsal Attention Network (DAN), Anterior Insula Network (AIN), Auditory-Sensory-Motor Network (ASMN) and Medial Visual Network (MVN). The DMN was selected visually, as the unique cluster generating the typical resting-state pattern of anterior and posterior cingulate cortex (ACC and PCC respectively) and bilateral inferior parietal cortex coactivation. The reduced FC in ASD group involves DMN medial nodes: frontal lobe (peak Talairach [TAL] coordinates -1, 49, -6; cluster size 6655 mm^3) and PCC (peak TAL coordinates -7, -41, 12; cluster size 5975 mm^3). The enhanced FC involved precuneus and lateral DMN nodes: right parietal lobe (peak TAL coordinates 44, -50, 27; cluster size 6048 mm^3) and left parietal lobe (peak TAL coordinates -28, -61, 45; cluster size 1186 mm^3) (**Fig.1**). All the clusters survived a more conservative statistical threshold ($p < 0.005$), except for the cluster of FC enhancement in the precuneus in the ASD group.

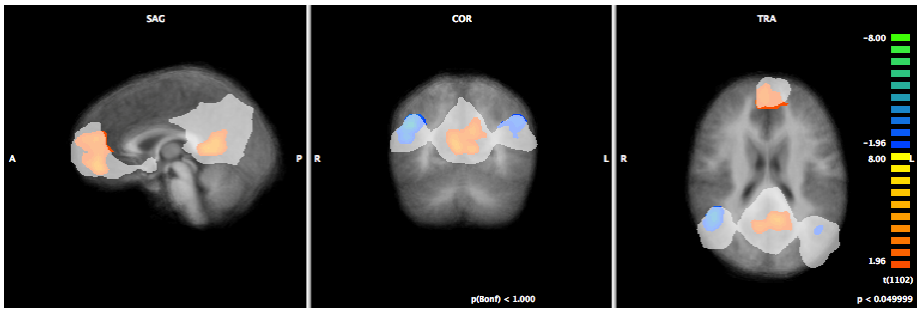

Fig.1 DMN area of reduced FC in ASD vs TD (in orange); DMN areas of enhanced FC in ASD vs TD (in blue); statistical threshold was set at $p < 0.05$, multiple compatisons corrected.

Discussion and conclusions: Our current findings on ASD children are in agreement with both previously published studies of DMN hypo-connectivity (in adults and adolescents with ASD) and recently published Uddin's paper that revealed only hyper-connectivity in ASD children [(4)]: a unified view of DMN FC characterized by both enhancement and reduction is here reported. By supposing that the enhancement in DMN FC in ASD is not generalized to all nodes, but limited to the FC of the precuneus and the parietal cortex, we hypothesize a possible methodological explanation to the variability in literature results. Regardless the analysis methods, we assume that all the alterations in RSNs FC represent a change in cognitive states. In particular, the DMN seems to be implicated in Theory of Mind, episodic memory and other self-reflective processes [(8)]. fMRI literature on parietal cortex link this area to integration of visual and motor information, attention, visuospatial processing and Theory of Mind [(9)]. Both enhancement and reduction in DMN FC could represent aberration. Under the relationship hypothesis between "extrinsic" fMRI activity and "instrinsic" RSfMRI FC, we suppose that the FC enhancement in DMN parietal nodes could nullify or reduce the "extrinsic" parietal cortex normal functions. Within-network hyperconnectivity may also reduce the interaction among networks and could be a barrier for the "normal activity" of neuronal functionally related regions. On the other side, we hypothesize that FC reduction within DMN could be the effect of enhanced activity with others areas outside the network. As a future purpose we would like to investigate, by means of seed-based analysis on an independent sample, the FC of each of the DMN nodes altered in our ICA analysis in order to study the "directions" of this aberration and to make a robust interpretation of present results.

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