Characterization of structural and functional brain impairment and phenotypic association in autism spectrum disorder

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PURPOSE: The inferior frontal gyrus (IFG) had recently been found to be abnormal in autism spectrum disorder (ASD), especially the mirror neurons within the IFG and their projections that function in normal social communication and language development [1]. There are usually impaired behaviors (e.g., repetition or lack of impulsivity control) together with the underdeveloped intelligence in especially children population with ASD compared to the typically developing children [2]. The purpose of this study is to study the changes of the structure, functional connectivity and activity of two primary sub-segments of inferior frontal as well as the subcortical caudate regions in autistic children.

MATERIALS AND METHODS: Data were downloaded from a multi-center Functional Connectome Project which released over 500 autism MRI data (http://www.nitrc.org/projects/fcon_1000). 127 children with ASD (average age: 13.5±6.0 years) and 153 age-matched typically developing children as controls (average age: 14.5±5.7 years) from the NYU/Yale/Stanford centers were selected based on the average and range of ages of participants. 3D high resolution T1-MPRAGE (image size=160x256x256, resolution=1x1x1mm^3) and resting state (RS)-fMRI using a gradient echo EPI sequence (TR=2000msec, resolution=3x3x4mm^3, 180 volumes) with 33 slices cover the entire cerebrum were downloaded. Functional connectivity network from three seeds, namely, the bilateral triangularis ortibo-part and the opercularis part of IFG, and the caudate in the MNI 2mm template space were derived. Preprocessing steps for RS-fMRI data included realignment, spatial gauss smoothing with full width at half maximum (FWHM)=6mm, band pass temporal filtering 0.005-0.1Hz, co-registration to MPRAGE and removal of nuisance signals (motion parameters, the global signal, and signals derived from cerebrospinal fluid and white matter), and transformation to MNI standard space. The anatomical and functional data were preprocessed using both FMRIB Software Library (FSL) (e.g. tissue segmentation, registration, smoothing, and regression) and Analysis of Functional NeuroImages (AFNI) (i.e. re-orientation, skull stripping, motion correction, filtering, ROI time courses extraction). Volumetric whole-brain voxel-based morphometry (VBM) package in FSL was used (http://www.fmrib.ox.ac.uk/fsl/vbm) for structural gray matter density analysis. The fractional amplitude of low frequency fluctuation (fALFF) of fMRI data at 0.08-0.1Hz was analyzed in FSL. The total number of voxels (N) and average correlational z-value (Z) were computed from the functional connectivity map of each seed using a threshold of cluster corrected P<0.05. The N and Z were used to correlate with multiple phenotypic data including the Autism Diagnostic Observation Schedule (ADOS), the Autism Diagnostic Interview, Revised (ADI-R) and intelligent quotient (IQ) tests.

RESULTS: There were significant alterations of functional connectivity patterns in children with ASD compared to age-matched controls in both datasets; seeding from the caudate and IFG (minimum Z>2.3; cluster significance, P<0.05, corrected) (*Figure1 A-C*). Base on VBM results, there were significant regional brain atrophies including IFG and superior temporal cortices in ASD compared to controls (FSL TCFE corrected P<0.005) (*Figure1 D)*. In addition, the fALFF reflecting spontaneous neuronal activity was reduced in the caudate and IFG region.

There was significant correlation between either N or Z connected from caudate and full scale of IQ evaluation in children with ASD (r=-0.47, P=0.034). And correlations were found between number of connections from IFG seeds and ADOS /ADI-R tests (P<0.05, *Table 1*) as well.

fMRI metrics	Tests	r	p
Caudate (N & Z)	IQ (full)	-0.47	0.034
IFG triangularis (N)	ADOS module	-0.57	0.0016
IFG triangularis (N)	ADOS total	-0.46	0.014
IFG triangularis (N)	ADOS communication	-0.47	0.04
IFG triangularis (N)	ADI-R research	-0.47	0.04
IFG opercularis (N)	ADOS module	-0.64	0.0002
IFG opercularis (N)	ADOS total	-0.50	0.007

Table1. Correlations between fMRI metric and phenotypic data.

CONCLUSIONS: We had demonstrated regional atrophy, abnormal functional connectivity and reduced spontaneous neuronal activity of caudate and IFG in children with ASD. Consistent with [3], there were significant associations between altered brain functional connectivity and phenotypic impairment in autistic children. Further confirmation with task-related neuroimaging studies is warranted in the future.

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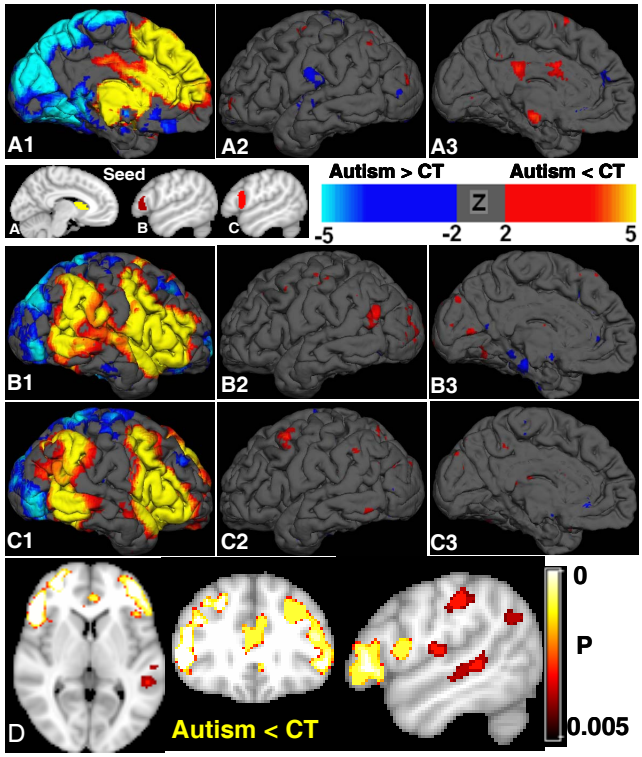

Figure1. Functional connectivity network seeding from caudate in controls (CT) (**A1**) showed positive connections with the frontal and subcortical regions; but negative connections with the posterior visual and parietal areas. Difference of connectivity pattern comparing children with ASD (Autism) to controls seeded from caudate were shown in A2 (lateral) and A3 (medial) with a primary reduction of cingulum and middle temporal connectivity in autism (red) and increments in several regions including the inferior frontal areas (blue). Functional connectivity network seeding from the triangle IFG in controls in (**B1**): positive connections with the frontal and temporal regions; negative connections with the posterior visual and superior parietal areas. Difference of connectivity pattern comparing autism to controls seeded from triangle IFG were shown in B2 and B3 with some reductions of visual and temporal connectivity in autism (red) and increments in the regions including medial temporal areas (blue). Functional connectivity seeding from opercular IFG was shown in **C1**-C3; with mainly decreased connectivity in autism in the superior frontal regions. Seed regions are shown in the upper left images; and all statistical results are obtained with the threshold of minimal Z>2.3; cluster significance, P<0.05, corrected. **D**: VBM results comparing ASD to control showed most significant brain atrophies in the IFG regions (cluster corrected P<0.005).

References. [1] Bastiaanssen et al. Biol. Psychiatry. 2011:832-8. [2] Lacoboni et al. Ann Neurol. 2007:213-8. [3] Enticott et al Biol. Psychiatry. 2012:427-433.