Revealing Morphological Connectome Alternation in Autistic Brain

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Introduction: Autism is a complex developmental disability that causes problems with social interaction, language and communication, and repetitive stereotyped behaviors and restricted interests. According to the latest estimate released in 2012 by the Centers for Disease Control and Prevention (CDC), autism affected 1 in 88 American children. Although great heterogeneity exists, previous findings from structural and functional aspects suggest that autism has atypical brain connectivity patterns. Recently, human brain connectome has become a popular technique that investigates brain connectivity at a network level [1]. In particular, human brain can be considered as a complex network with brain regions as nodes and inter-regional interactions as edges. One of the most important properties of the brain network is that it generally composes several modules, e.g., community structures, which are more densely connected within modules than between the modules. In this study, we propose to use modern human brain connectome techniques to investigate brain morphological networks constructed from MR images of autistic children, and compare their modular organization with those derived from age- and gender-matched typically developed controls.

Methods: Participants of this study were selected from National Database for Autism Research (NDAR, http://ndar.nih.gov), including 49 autistic children and 51 typically developed controls (Table 1). T1-weighted brain MR images were collected using 1.5T MR scanners. Image processing was performed with the Freesurfer suite (http://surfer.nmr.mgh.harvard.edu). Briefly, all MR images were skull stripped and tissue segmented. Inner (grey-white matter interface) and outer (grey matter-CSF interface) cortical surfaces were constructed and their distance was measured as cortical thickness for each vertex. By registering the Desikan-Killiany cortical atlas [2] to each subject, the brain was parcellated into 68 cortical regions, which serve as nodes for the brain network. We then define the edges between each pair of nodes as their inter-regional correlations of cortical thickness across the population [3]. Note that before correlation, a linear regression was performed at the raw cortical thickness in each ROI to remove the effects of mean cortical thickness, age, gender, and age-gender interaction. Finally, a structural cortical network was constructed with *N* (68) nodes and *K* (2278=68*67/2) weighted edges for autism and control, respectively. For group comparison, edge weights in each network were normalized by their total network weights.

Table 1. Demographics of Participants.

	Number	Gender* (M/F)	Age* (years)
Autism	49	40/9	9.6±2.2
Control	51	39/12	9.7±2.1

*No significant difference between two groups

Human brain connectome techniques were applied to study the modular organization of brain networks derived from their correlation matrices [1]. An optimum network partition is determined at each network for achieving the maximum network modularity, which measures the extent to which the modules are densely intra-connected and sparsely inter-connected. Intra-module connectivity is defined as the sum of edge weights within each module, and inter-module connectivity is computed as the sum of edge weights between a pair of modules. The statistical significance of the network measure difference between groups was performed using a non-parametric permutation test method. Meanwhile, the correlation matrices of the two groups were compared after Fisher's r-to-z transformation, to find the connections with significantly different correlation strength in autism. To correct for multiple comparison, false discovery rate (FDR) was employed.

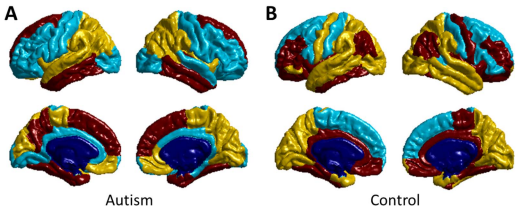

Fig. 1. Modular organization of autistic children and typically developed control. Colors in each group represent cortical regions in the same module, respectively.

Results: Three modules were found in autistic brain (Fig. 1A), as module Ⅰ – executive strategic/sensorimotor/visual, module Ⅱ – spatial and auditory, module Ⅲ – recognition and self-awareness. Similarly, we found three modules in control brain (Fig. 1B), as module Ⅰ – executive strategic, module Ⅱ – spatial/auditory/visual, module Ⅲ – self-reference and episodic memory.

We take the modular organization in control as baseline [4], and the network comparisons between autism and control are thus focused on the same modular organization (Fig. 1B) derived from the control. The comparison yields a significant reduced modularity in the autism (Fig. 2A). We also found that autism demonstrated significant lower intra-module connectivity in both modules Ⅰ and Ⅱ, while surprisingly higher connectivity in module Ⅲ (Fig. 2B). Autism shows more inter-module connections as expected, mainly in modules Ⅱ-Ⅲ, and Ⅰ-Ⅲ (Fig. 2C). The inter-regional correlation strength was also examined (p<0.01, FDR corrected) (Fig. 3). We found that the connections with increased correlation strength were mainly located within frontal lobe, while the decreased correlations were between frontal lobe and regions in parietal, temporal, and limbic lobes.

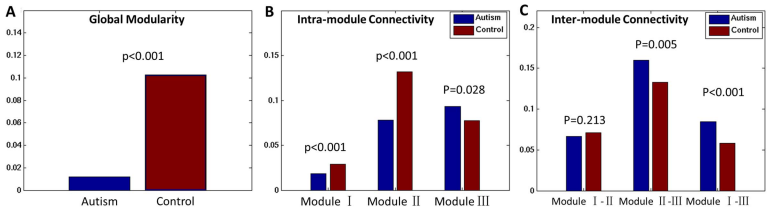

Fig. 2. Comparisons of autism and control in terms of Global modularity (A), intra-module connectivity (B), and inter-module connectivity (C).

Discussion: Our main findings are as follows: 1) When compared with control, autism presented a significantly reduced modularity, which may rise from a re-organization of the brain network; 2) Increased intra- and inter-module connectivity were both found in autism among the module Ⅲ. This finding suggests a weight distribution alternation in autistic brain, and it may be interpreted as a compensatory strategy that autism focuses more on these cortical regions to remedy their deficits on self-related functions [5]; 3) Inter-regional correlations in autism were revealed with the increased intra-connections in the frontal lobe, while the decreased connections between frontal lobe and other lobes, which are agreed with previous studies [6] and may contribute to the alternation of modular organization. In general, the present study provides insightful implications on the understanding of alternation of brain connectome in autistic children.

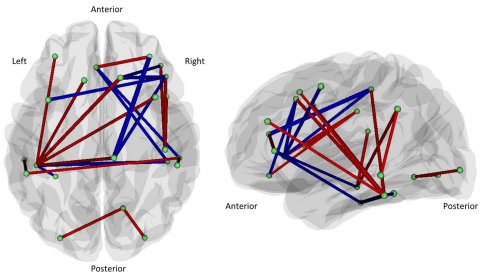

Fig. 3. Visualization of connections in axial view (left) and sagittal view (right) with significantly lower (red) and higher (blue) regional correlation strength in the autistic brain, compared to that of control.

References: [1]. Rubinov M, Sporns O, NeuroImage 52:1059-1069, 2009.. [2]. Desikan RS, et al., NeuroImage 31:968-980, 2006. [3]. He Y, et al., Cerebral Cortex 17:2407-2419, 2007. [4]. Chen ZJ, et al., NeuroImage 56:235-245, 2011. [5]. Ben Shalom D, et al., Journal of autism and developmental disorders 36:395-400, 2006. [6]. Barttfeld P, et al., Neuropsychologia 49:254-263, 2011.