Diffusion MRI identifies enhanced connection of neural pathways in toddlers with Autism Spectrum Disorder

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Introduction: Autism Spectrum Disorder (ASD) is a heterogeneous group of neuro-developmental diseases affecting 1 in 68 children in the USA, and is characterized by impairment in socio-communicative abilities, as well as restricted and stereotyped behaviours. There is a growing interest in identifying structural and functional neuro-anatomical correlates of the disorder, since detecting key relationships within different brain regions has the potential to add predictive power to early behavioural assessment, with a profound impact on tailored rehabilitation intervention. Advanced connectivity studies focussing on early developmental stage reported disrupted connectivity in children with ASD compared to typical peers[1]. Interesting findings include the "over connectivity" within specific neural networks in ASD participants when compared to infants with developmental delay (DD)[2] and a rightward bias in asymmetry in ASD in higher-order association areas[3].

In this study we analyse the diffusion MRI of ASD and DD infants below 36 months of age and compare the differences in neural pathways using network based statistics (NBS). Further we analyse the asymmetry between the two cohorts from the obtained neural pathways.

Method: As part of an ongoing prospective study, children with neuro-developmental disorder (NDD) were recruited from January 2012 in a tertiary care children's hospital. Subjects were included in the study if they satisfied the following criteria: a) have been clinically diagnosed with NDD, b) were aged less than 36 months, c) had no neuro-metabolic or genetic syndromes and, d) undergone a brain MRI. A total of 59 subjects with NDD fulfilled our inclusion criteria. The cohort was further divided into two groups, based on clinical assessment i.e. ASD (n=39; mean age=27 months) and only DD (n=20; mean age=30 months) i.e. without any sign of ASD.

Brain MRIs were acquired on a 1.5T GE scanner. High angular resolution diffusion imaging (HARDI) scans were acquired in 31 directions (b=1000 s/mm^2). An extensive preprocessing procedure was followed to detect and correct for image artefacts caused by involuntary head motion, cardiac pulsation, and image distortions for the diffusion-weighted images[4,5]. Image post-processing consisted of cortical parcellation of the T1 images by registering[6] an infant AAL (anatomical atlas labelling) atlas[7] from UNC Chapel Hill, North Carolina, USA into 90 regions excluding the cerebellum. The segmentation of the brain tissues into gray matter (GM), white-matter (WM) and cerebrospinal fluid (CSF) was performed using an in-house implementation[8]. The partial volume estimation maps were then generated[9] to extract the GM/WM interface for the tractography seeding strategy. Whole brain probabilistic tractography was performed using the Anatomically Constrained Tractography (ACT) framework of MRtrix[10,11]. Further, (spherical-deconvolution informed filtered tractograms) SIFT[12] was employed to reduce bias over longer streamlines and improve quantification of streamline number as a measure of structural connectivity[16]. Using this approach, 90×90 network connectivity matrices were built by encoding the post-SIFT streamline numbers (D_i) connecting each pair of cortical/sub-cortical regions. The connectivity matrices of the ASD and DD groups were then contrasted for a group-wise comparison using NBS[13]. NBS performs a graph-based clustering involving generalized linear model to find clusters of network connections that are significantly different between the groups. A *t*-threshold of 3.1 with 5000 permutations and $p<0.05$ were chosen for the NBS group-wise comparison. The intrahemispheric connections that were significantly different in NBS were further analysed for asymmetry in the ASD and DD groups by computing the lateralization indices[14] (LI) = (D_i(left) - D_i(right)) / (D_i(left) + D_i(right)).

Results: The group-wise comparison of the network connections with NBS revealed an over-connectivity in ASD when compared to DD with two distinct sub-networks (Fig. 1) (p=0.023 & p=0.008) centered on superior temporal gyrus (both hemispheres) and middle temporal gyrus (right hemisphere). No over-connectivity in the DD group was observed. On further computation of LI indices of the 6-pairs of significantly different intra-hemispheric connections (Fig. 2), we found that ASD group possessed an inverse rightward bias in the asymmetry (LI = -0.15±0.33) when compared to the DD group (LI = 0.05±0.33) for the connections between middle temporal gyrus and caudate nucleus. The connections between superior temporal gyrus and caudate nucleus also showed a rightward bias for the ASD (LI = -0.11±0.32) vs. DD (LI = -0.09±0.45) groups, while ASD had a reduced leftward bias compared to DD for the connections between the supramarginal gyrus and middle temporal gyrus.

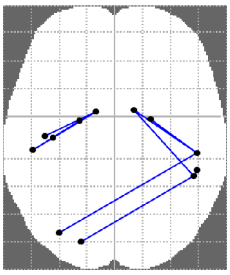

Fig. 1 Significant network differences with NBS (t=3.1, p<0.05) between ASD and DD groups.

Discussions: The over-connectivity observed in the ASD young children may be related to brain overgrowth as previously reported[2,15]. It is however of interest that we found abnormalities in the temporal regions known to be associated with social perception, behavioral and cognitive deficits. The rightward asymmetry bias in the ASD group for the superior temporal and middle temporal gyri to caudate nucleus show some convergence with previous studies reporting loss of leftward asymmetry in ASD adolescents and adults[3]. The LI results must be interpreted carefully. In this study, infants with ASD were compared with a DD group, which may not accurately reflect the characteristics of the normative population. Therefore, rightward asymmetry associated with superior temporal gyri and putamen observed both in ASD and DD groups suggest possible language and cognitive deficits associated with NDD in general. Thus, further studies with larger and more diverse cohorts will be required to verify these findings.

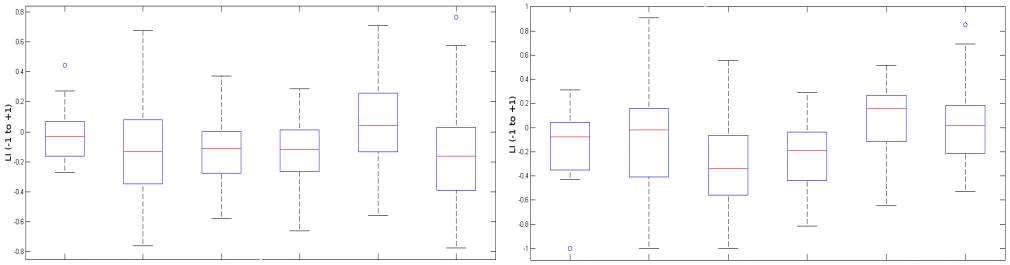

Fig. 2. Lateralization indices for ASD (left) and DD (right) groups for the connections in the following order from left to right: PreCG-Caudate, Caudate-Sup_TempG, Rol_Operculum-Caudate, Putamen-Sup_TempG, SupraMarG-Mid_TempG, Caudate-Mid_TempG.

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