Connectomics of High Functioning Autism Spectrum Disorder

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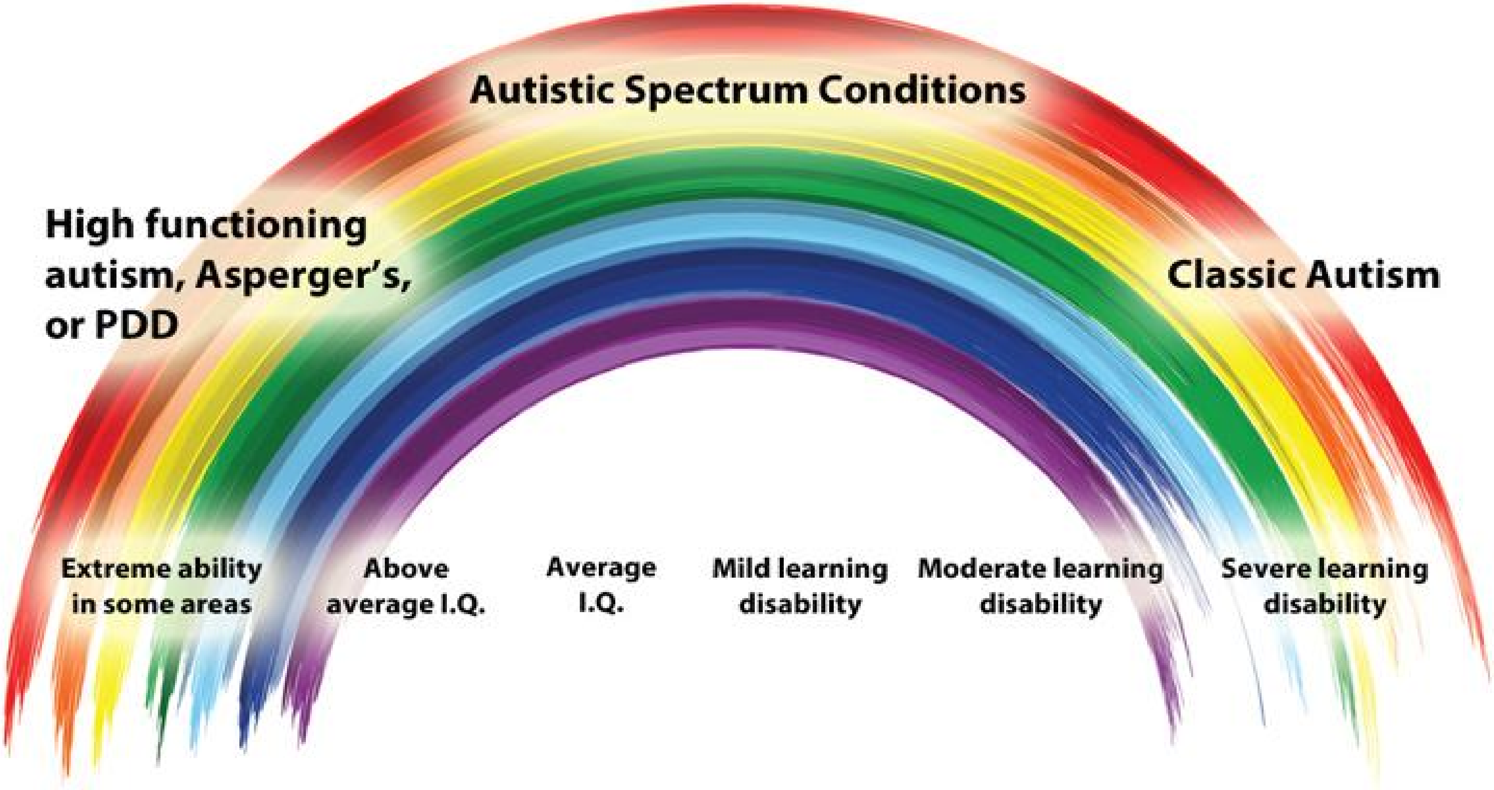
The What?


Autistic Spectrum Conditions
High functioning autism, Asperger's, or PDD
Classic Autism
Extreme ability in some areas
Above average I.Q.
Average I.Q.
Mild learning disability
Moderate learning disability
Severe learning disability

High Functioning Autism

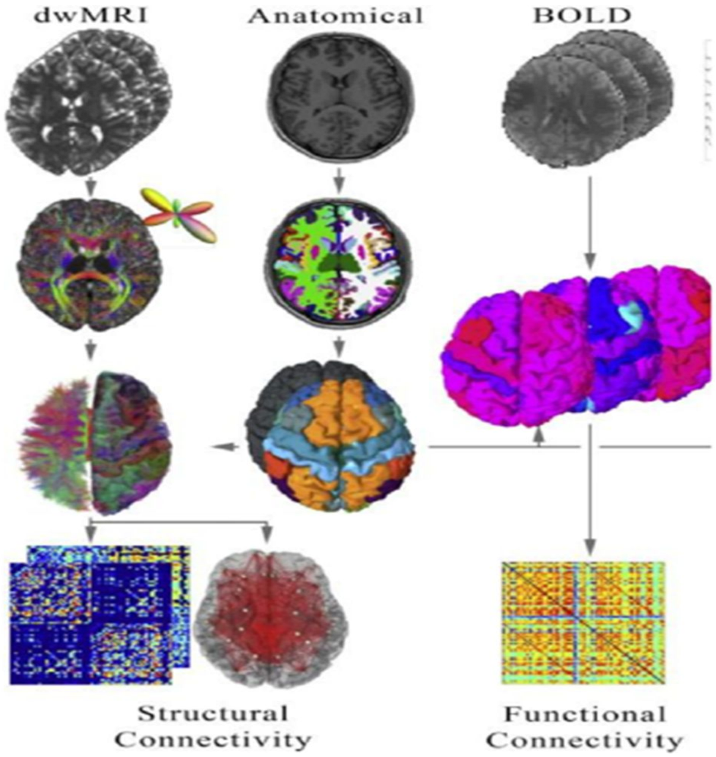
- High IQ
- Difficulty with Language & Social Communication
- Repetitive or Restrictive behaviours
- Impairment of ‘Theory of Mind’
- The Disorder of ‘Functional Integration’

Autism as a ‘connectivity disorder’[6]

Connectivity from Neuroimaging Data

- ❑ T1- weighted images
  - ➢ Anatomical/ Functional Parcellation
- ❑ Diffusion Weighted MRI
  - ➢ Probabilistic/Deterministic Tractography
  - ➢ Number of connected Fibres
  - ➢ Fractional Anisotropy
- ➢ Resting State Functional MRI
  - ➢ Mean BOLD time-series of ROIs
  - ➢ Pairwise Pearson Correlations

Image Courtesy : The Virtual Brain[1]



Data (umcd.humanconnectomeproject.org) [2]

Resting State Functional MRI

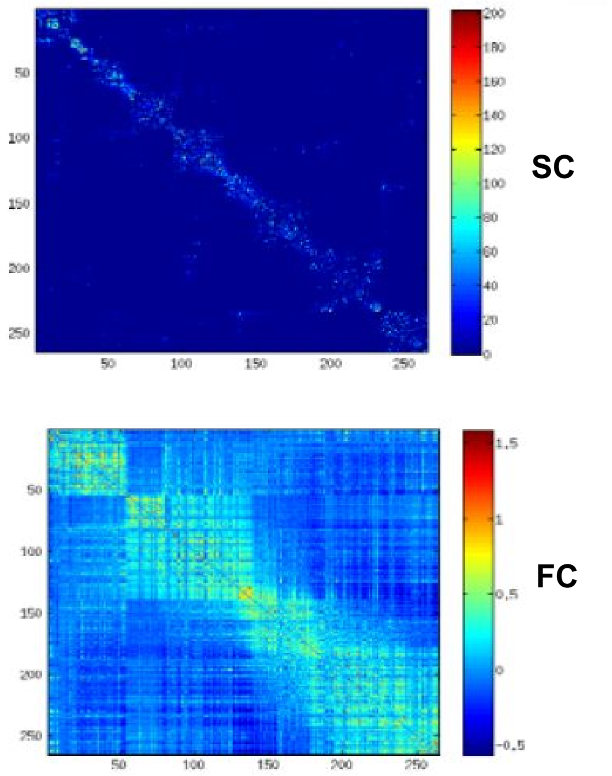
37 TD (age: 13 2, 9.5 –17.8 years) and
41 ASD (13.5 2.4, 9.3–17.9 years)

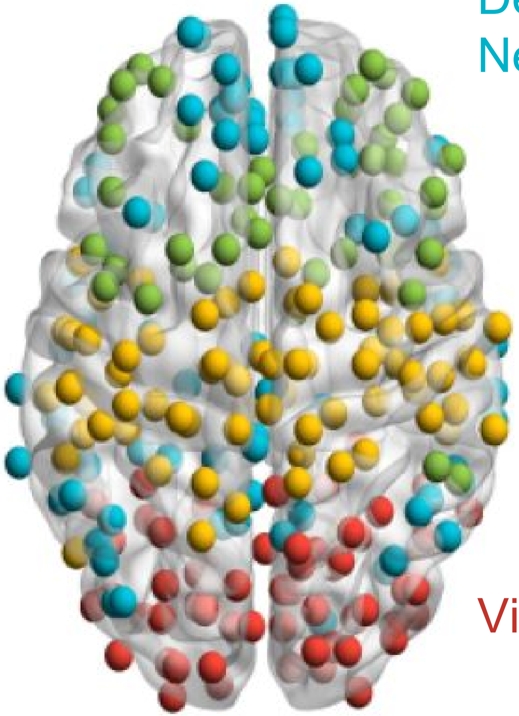
Diffusion Tensor Imaging

43 TD (age: 13.1 2.4, 9.0–18.0 years) and
51 ASD (13.0 2:8, 8.4–18.2 years)

All subjects were age, gender and IQ matched.

Connectomes





Anatomical Connectivity

TD>ASD (t-test , FDR corrected, p<0.05)

Left Hippocampus	Right Superior Occipital	3.41**
Left Posterior Cingulate	Right Superior Occipital	3.51**
Right Thalamus	Right Posterior Parahippocampal	4.61
Right Precentral Cortex	Right Superior Frontal Gyrus	3.61
Right frontal pole	Left anterior cingulate cortex	3.22

TD<ASD (t-test , FDR corrected, p<0.05)

Right Putamen	Right Superior Parietal Lobule	3.56*

Functional Connectivity

TD>ASD (t-test , FDR corrected, $p<0.05$)

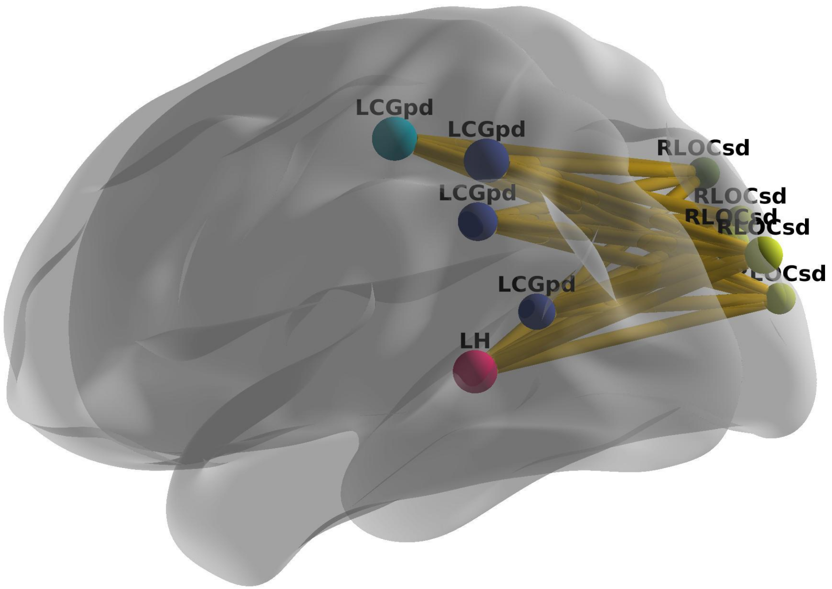
Right Frontal Orbital Cortex	Left Posterior Cingulate Gyrus	3.90**
Left Caudate	Left Paracingulate Gyrus	3.85**
Right precuneus	Left posterior cingulate cortex	3.70
Right Precentral Cortex	Right Postcentral Cortex	3.89
Left occipital fusiform gyrus	Left intracalcerine	3.09

TD<ASD (t-test , FDR corrected, $p<0.05$)

Right Paracingulate	Left Lobule VI of Cerebellum	3.94**
Left Precuneus	Left Frontal Pole	3.58
Right Middle Temporal-occipital	Right Anterior Superior Temporal	3.05
Right Putamen	Right Superior Parietal Lobule	3.14

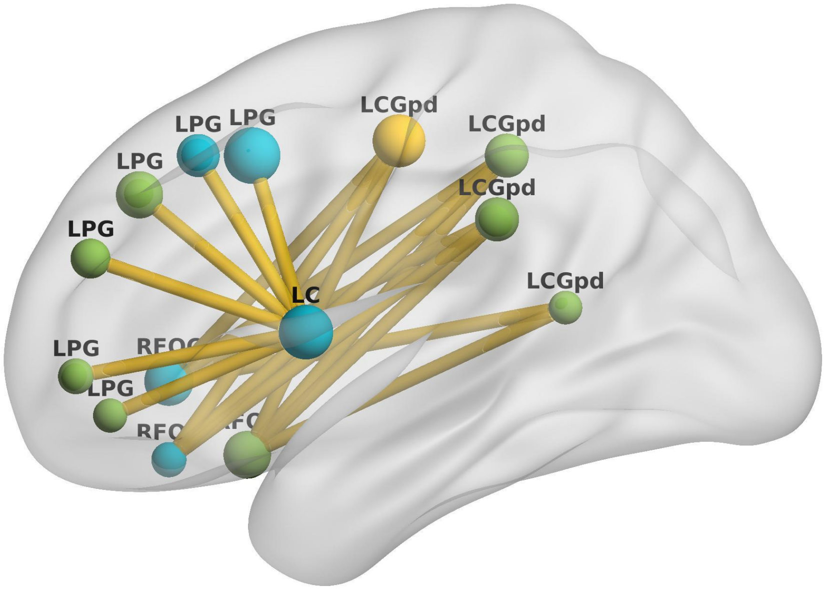
SC (TD>ASD)

LCGpd: Left Posterior Cingulate
LH: Left Hippocampus
RLOCsd: Right Lateral Superior Occipital Cortex



FC (TD>ASD)

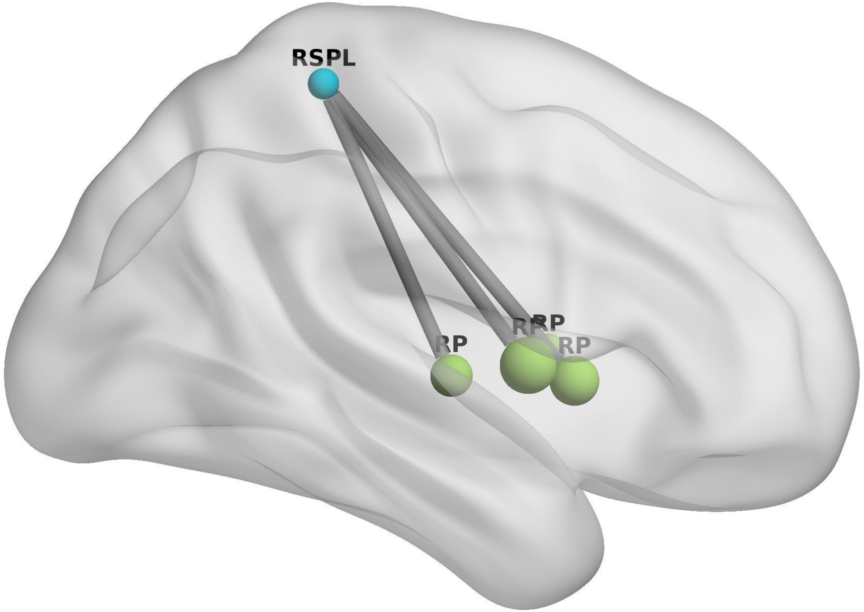
LPG: Left Paracingulate Gyrus
LC: Left Caudate
RFOG: Right Frontal Orbital Cortex



SC (ASD>TD)

RSPL: Right Superior Parietal Lobule

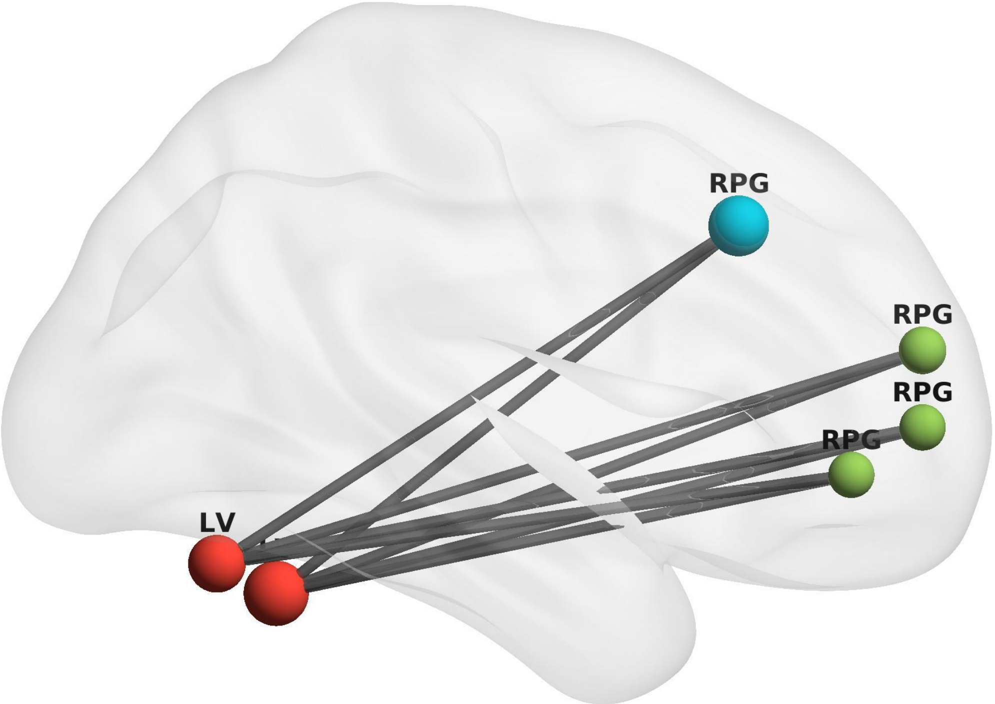
RP: Right Putamen



FC (ASD>TD)

RPG: Right Paracingulate Gyrus

LV: Left VI (Cerebellum)



Graph Theoretic Measures

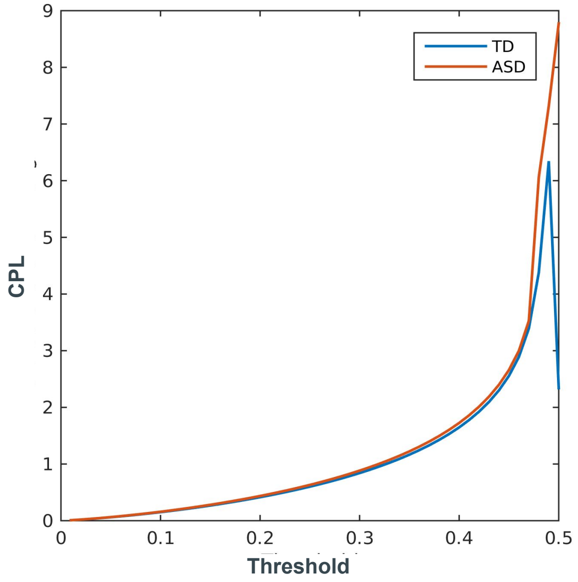
Global Efficiency: The inverse of the harmonic mean of shortest path length (dij) between each pair of nodes within the network.

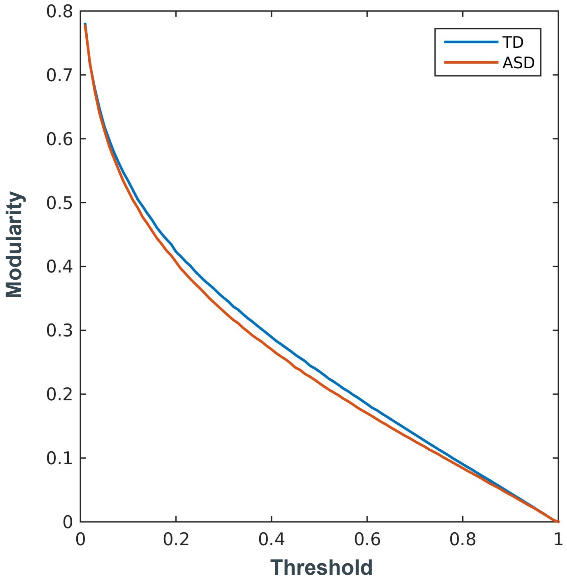
Local Efficiency: Average global efficiency of each node *i* of the sub-graph that contains neighbours of *i*. Measure of the fault tolerance of the system.

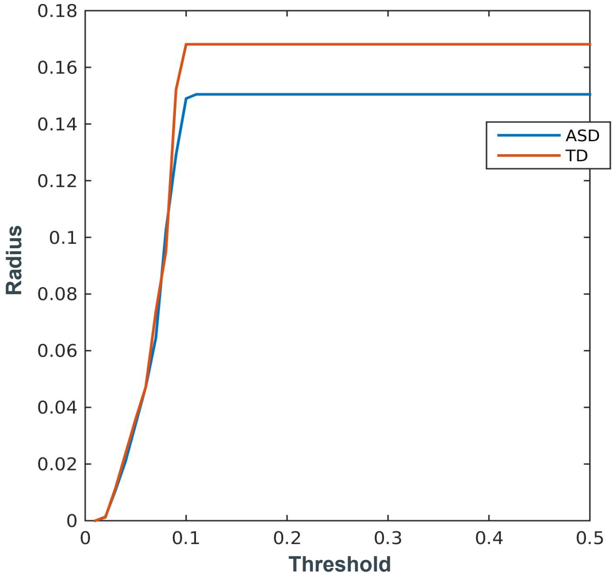
Characteristic Path Length: Average number of steps required along the shortest path to reach from any node of the graph to any other node.

Modularity: the fraction of the edges that fall within the given groups minus the expected such fraction if edges were distributed at random. .

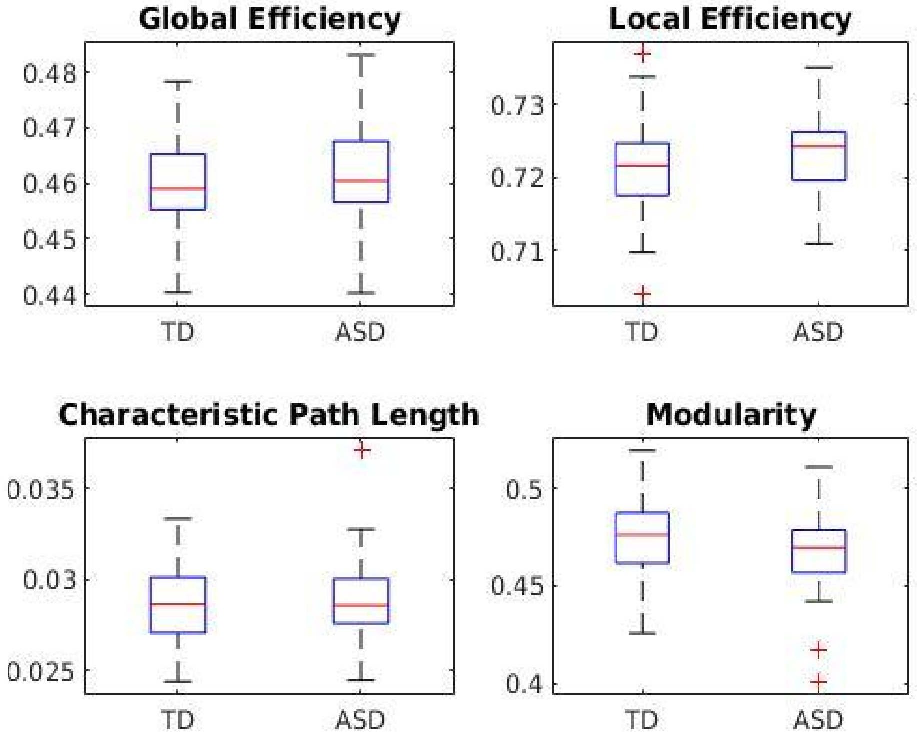
Issue of Thresholding







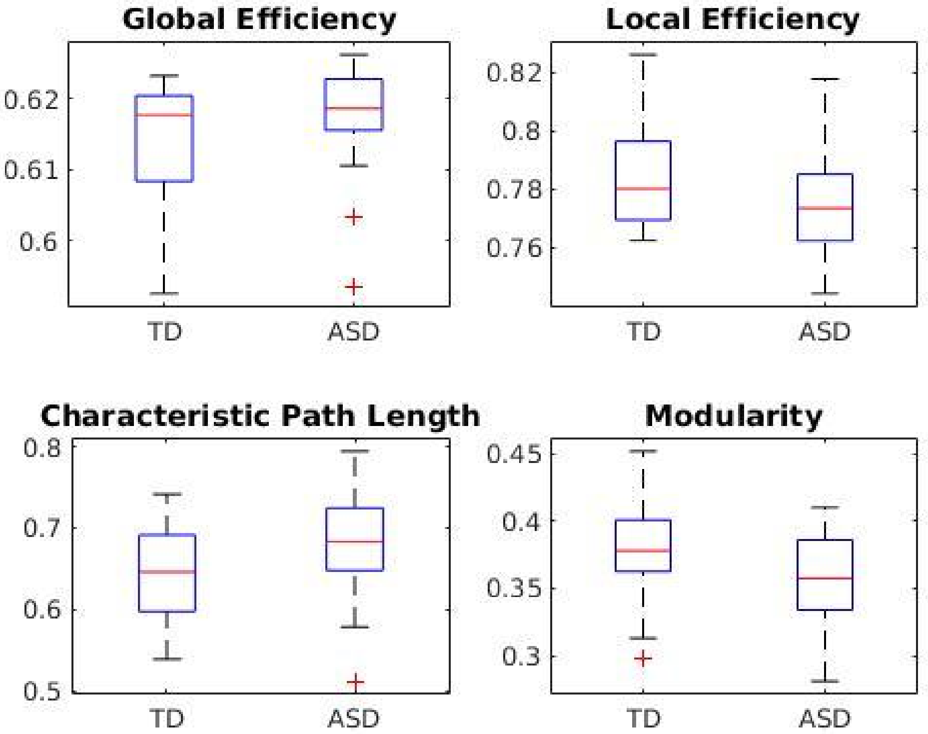
Anatomical Connectivity



Two-sided Wilcoxon rank-sum test

Network Measure	TD	ASD	p-value
Global Efficiency	0.4590	0.4604	0.14
Local Efficiency	0.7216	0.7242	0.036*
CPL	0.0286	0.0281	0.4
Modularity	0.4762	0.4697	0.079

Functional Connectivity



Two-sided Wilcoxon rank-sum test

Network Measure	TD	ASD	p-value
Global Efficiency	0.6178	0.6187	0.02
Local Efficiency	0.7803	0.7735	0.01
CPL	0.6461	0.6834	0.007
Modularity	0.3780	0.3573	0.005

Observations

- ➢ Structural under-connectivity between Default Mode Regions, anterior cingulate and higher order visual regions.
- ➢ Functional under-connectivity between Salience network and Default Mode regions. Functional over-connectivity in local connections in temporal lobe.
- ➢ Interhemispheric long-range connections are significantly lost than the intra-hemispheric connections.
- ➢ Less significant changes in anatomical graph topology, Increased global efficiency but decreased local efficiency of functional graphs.
- ➢ Average path length significantly increases, Modularity decreases. Number of global connections become stronger than local connections.

Implications

- ➢ Structural and functional under-connectivity of long range connections with posterior cingulate cortex:

"The abnormalities in cingulate responses during interpersonal interaction correlate with the severity of autistic symptoms, and the failure to show task dependent deactivation in the PCC correlates with overall social function."[3]

- ➢ Structural hyper-connectivity in SPL-Putamen along with functional hyper-connectivity between Cerebellum and right paracingulate cortex :

"Intact motor skill learning?[4] or Excitatory/ Inhibitory imbalance in the circuit ?"[5]

Implications

- Preserved Global Efficiency and impaired local efficiency in functional connectome, **but not in** structural connectome taken together with the long-range inter-module connectivity changes:

- Less Efficient[7-9] ? Compensatory[10]? Or Both?

- "An overconnected local network can be compared to a peninsula, separated from and with limited access to the rest of the brain, thereby creating long-distance underconnectivity. This may imply that the brain compensates for abnormal connectivity by incorporating areas that it has easier access to, such as the neighboring regions [10]"

What is it like to be High Functioning Autistic Child?

"... Imagine yourself in the vacuum. The stimuli *do* reach to you but you cannot really *engage* yourself with the stimuli."

- Practicing Psychologist

"...From a behavioral neurology perspective, the constellation suggests generalized dysfunction of the association cortex, with sparing of primary sensory and motor cortex and of white matter".

- The New Neurobiology of Autism : Cortex, Connectivity and Neuronal Organization

Future…

Rethinking segregation and integration: contributions of whole-brain modelling

Gustavo Deco, Giulio Tononi, Melanie Boly and Morten L. Kringelbach

Abstract | The brain regulates information flow by balancing the segregation and integration of incoming stimuli to facilitate flexible cognition and behaviour. The topological features of brain networks — in particular, network communities and hubs — support this segregation and integration but do not provide information about how external inputs are processed dynamically (that is, over time). Experiments in which the consequences of selective inputs on brain activity are controlled and traced with great precision could provide such information. However, such strategies have thus far had limited success. By contrast, recent whole-brain computational modelling approaches have enabled us to start assessing the effect of input perturbations on brain dynamics *in silico*.

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