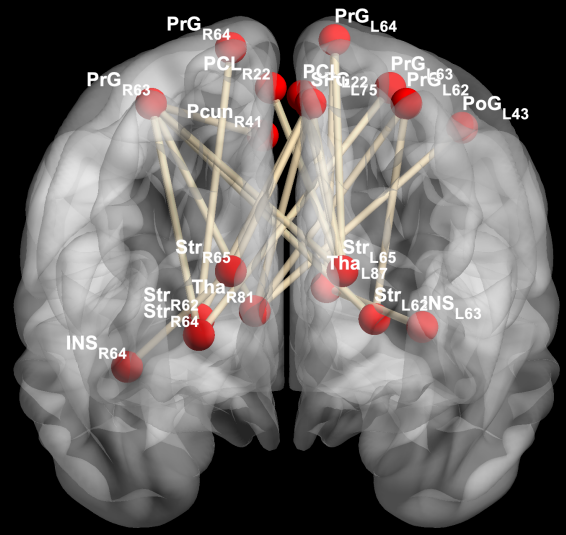
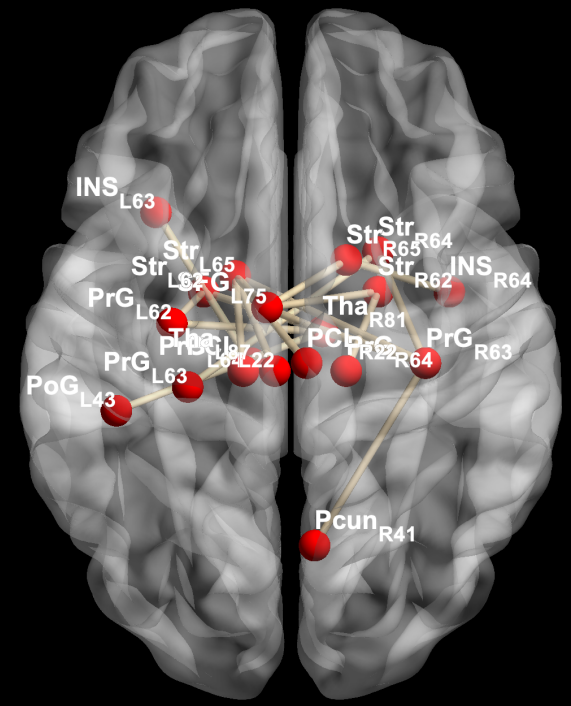
Brain networks.





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CS-E5700
Hands-on Network Analysis

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Background.

Our group has a background in bioinformation tech., neuroscience, and medicine.

- We want to learn how to model brain data/activity as a network from real-world data.
- How to calculate different network metrics and apply statistical tests?

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Brain network, connectome, contains neural connections in the brain.

- Scale can vary from the synaptic connections to inter-regional pathways.
- Functional connectome can be mapped with neuroimaging methods (fMRI, MEG etc.).
- Connectivity matrix: brain regions as nodes, time-series correlation as edge weights.

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What is the meaning of differences in connectomes?

- Differences are associated with experimental effects, medical conditions, and between-group differences.
- E.g. faulty wiring in psychiatric disorders or enchanted connectivity in some talented subpopulation.
- Connectome can be used as a tool for diagnostics.

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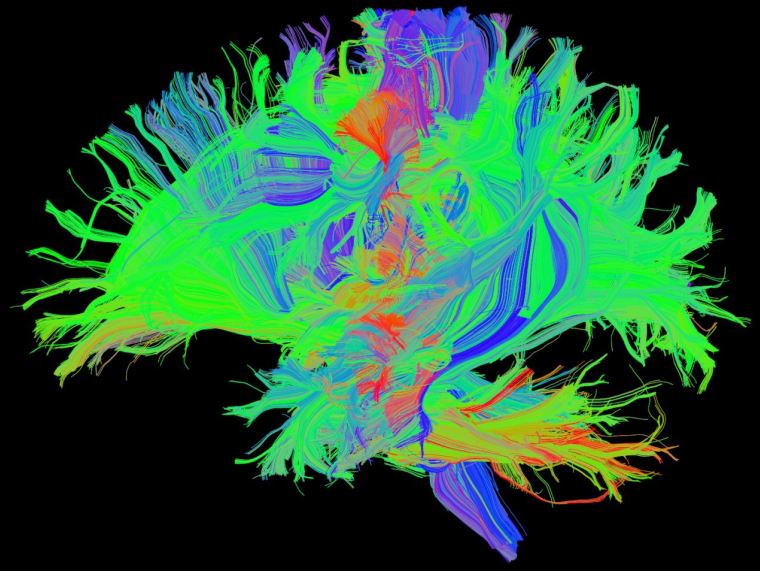
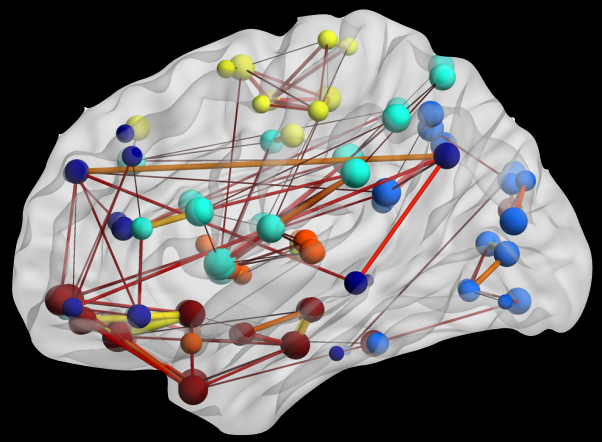
Fig 1: Human Brain Connectome



From https://perso.telecom-paristech.fr/comercier/

Fig 2: Functional brain network



From BrainNet Viewer. https://www.nitrc.org/project/list_screenshots.php?group_id=504&screenshot_id=381

- Structural networks are based on physical connections (neurons) measured with e.g. diffusion MRI.
- Links of the functional networks are not necessarily physical links (i.e. no neuron); they are mathematical models of the data.

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Autism spectrum disorder (ASD) is a developmental disorder.

- Neuroanatomically, pathological findings of autism are unspecific.
- ASD isn't a homogeneous disorder, and it has various causes and a vast range of functional symptoms.
  - We cannot generalize our results to the whole ASD.

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Our data was a selection from public Autism Brain Imaging Data Exchange (ABIDE) data set.

- We had resting-state fMRI from 47 ASD male patients with age, sex-matched neurotypical (NT) controls.
  - One subject pair was excluded from the analysis.

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Our goal was to find hyper- and hypoconnected links at ASD patients.

- Previous studies with the same data have found thalamocortical hyperconnectivity and amygdala-cortical.
- Can we reproduce the results?

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Networks.

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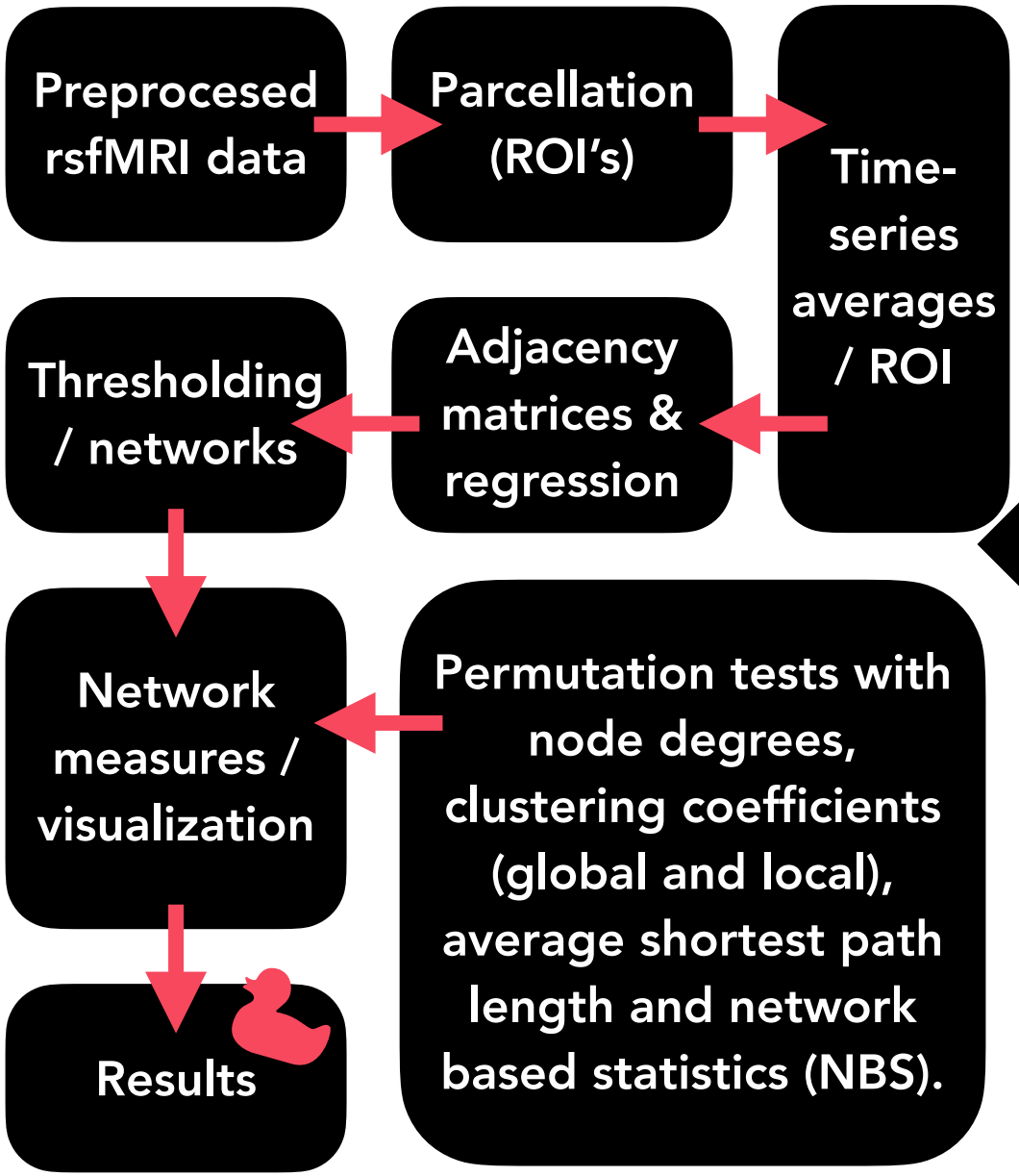
Flowchart of the project.



- We got already preprocessed resting-state fMRI data from the ABIDE data set.
- Preprocessing included the following steps:
  - Slice-timing and motion correction.
  - Nuisance signal regression and temporal filtering (0.009–0.1 Hz)
  - Normalization to MNI152 stereotactic space (2 mm^3 isotropic). It was done with linear and non-linear registrations.

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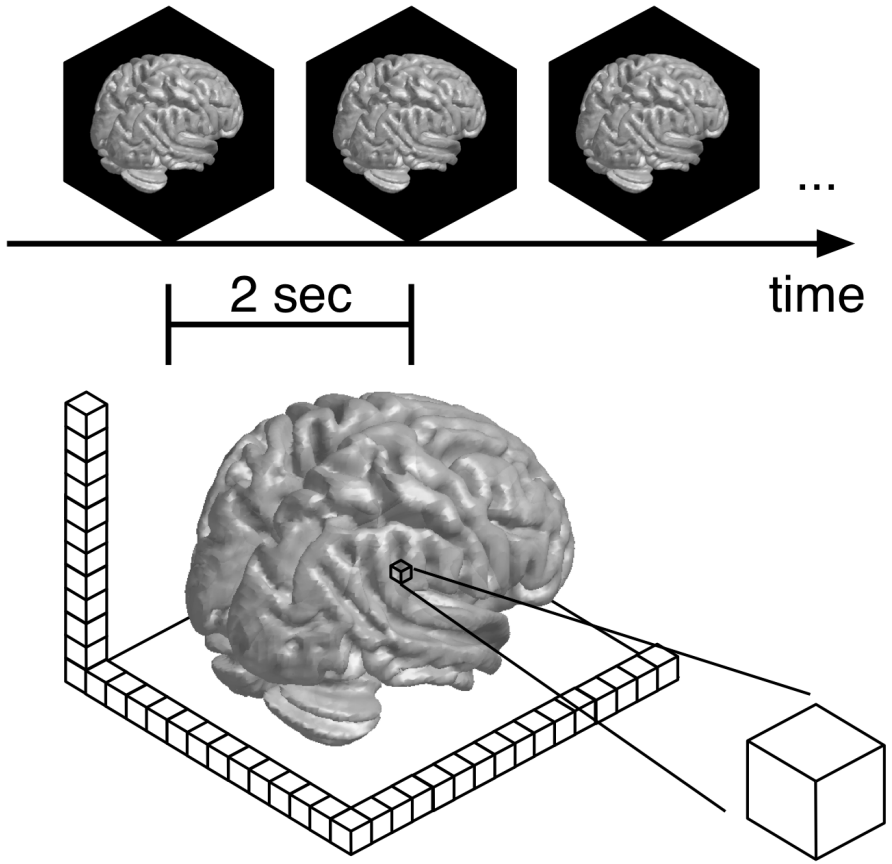

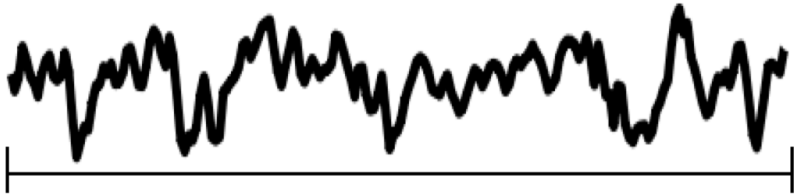

Single voxel Blood Oxygen Level (BOLD) signal

- Multiple *time series* are measured from different voxels at once.
- *Time series* can be considered independently or try to investigate mutual relationships.

Fig: Enrico Glerean (2017). NBE-E4530 *Special Course in Human Neuroscience*: Human brain connectivity

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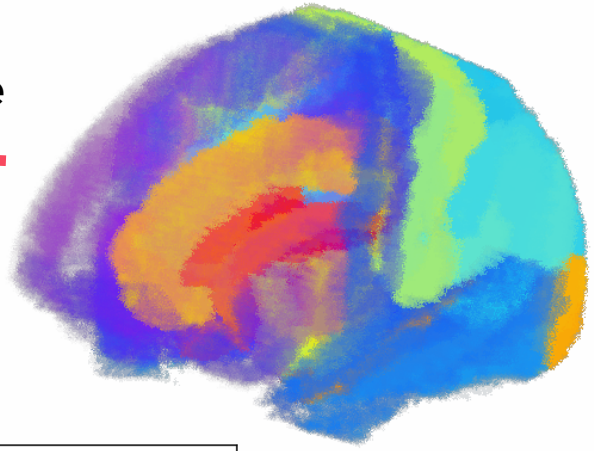
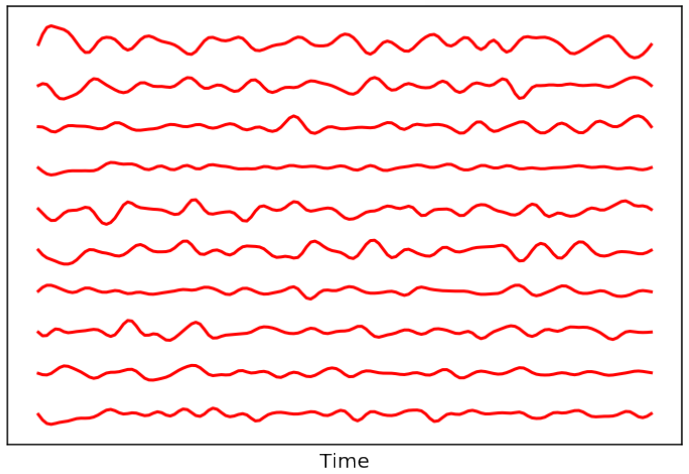
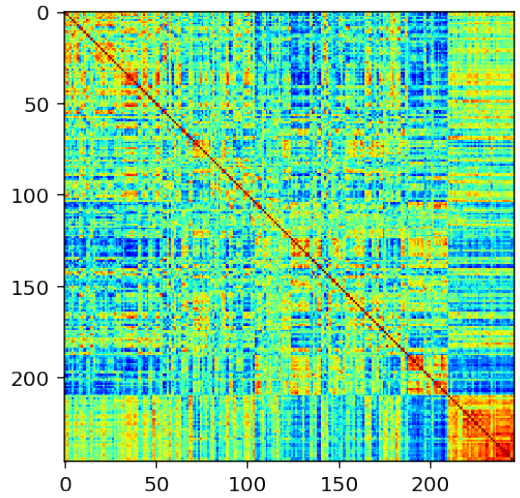
From parcellation we got ROI time series





Time-series correlations to adjacency matrix



- *Parcellation:* from 117,457 grey matter voxels to 246 ROI's.
- Correlations between *time series (ROI)* were computed.
- *Adjacency matrices* were created from the *correlation coefficients (link weights)* of the time series.
- Adjacency matrices hold the information of link weights between ROI's.

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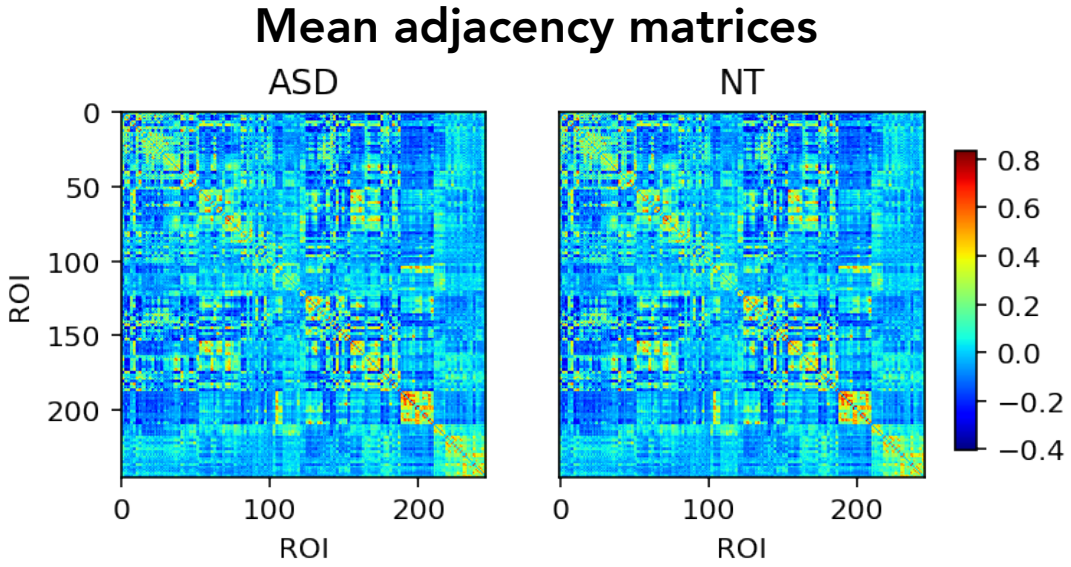

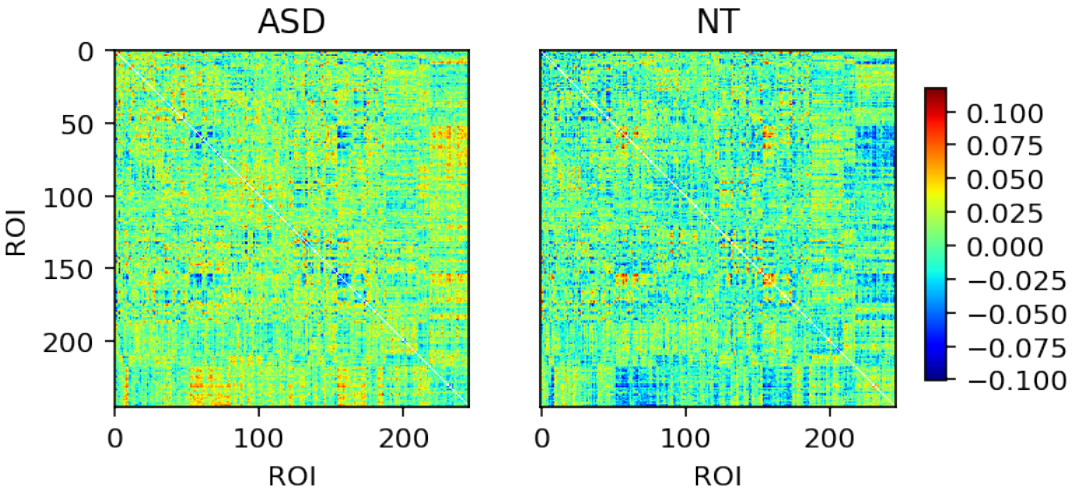

- Regression was used to tackle issues that arise from different imaging devices used in the data collection and movement of subjects.
- The effect of regression can be seen from the mean adjacency matrices.

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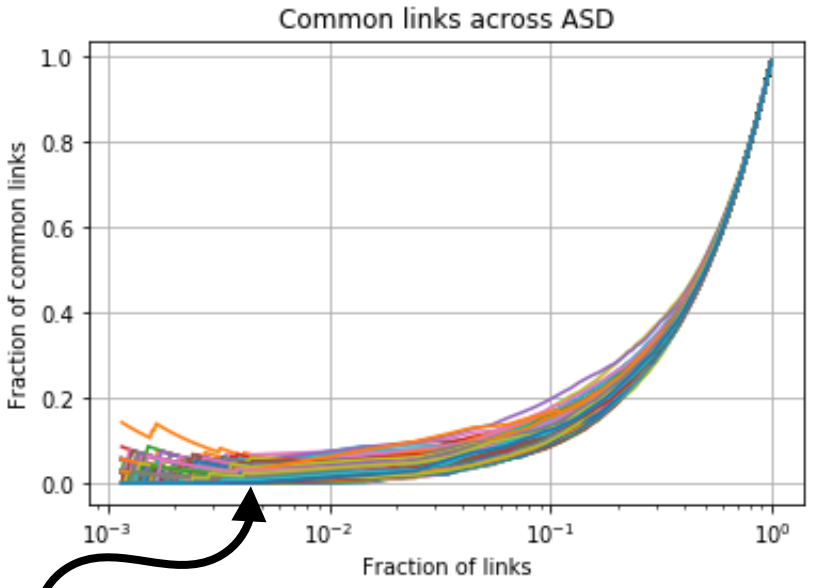
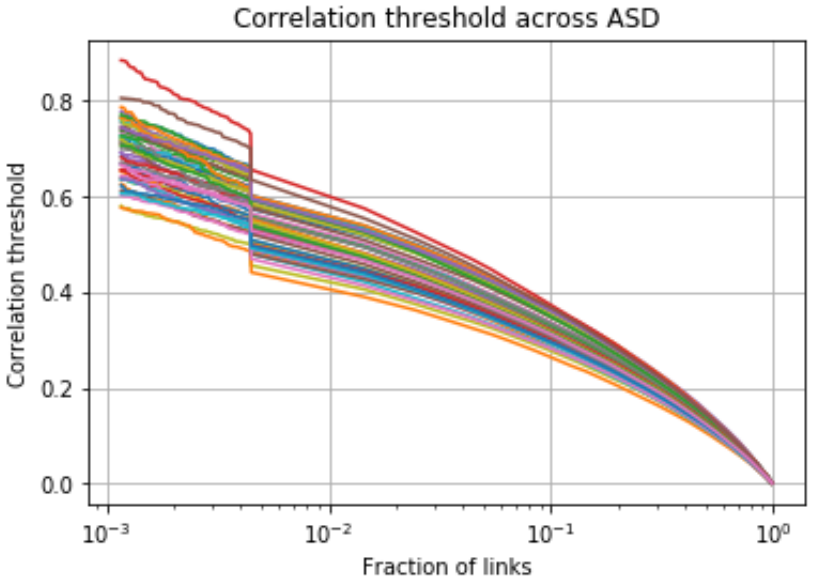


≈minimum



- Thresholding lets us focus only on the interesting part of the data and avoid heavy computation.
- There is not a single method to do thresholding.
- We wanted to optimize the threshold value to give the biggest difference between the two groups.
- 100 strongest links from each subject were chosen (≈minimum overlap).

* Similar figures done for neurotypicals

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Should the network be fully connected or not?

- The selection of only the 100 strongest links led to a loss of subcortical information.
- Fully connected network, MinST + 100 strongest provides information about subcortical – cortical connections.

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Using network properties as a diagnostic marker.

- **Degree distribution (node-wise):**
  - Compatible with the existence of hubs.
- **Clustering coefficient (node-wise):**
  - Measures how many neighbors of a node are connected to each other. Closely related to local efficiency.
- **Shortest path length (global-level):**
  - The average number of edges needed to get from any node in the network to any other node in the network. Inversely related to global efficiency.
- **Network-based statistic (NBS) (edge-wise):**
  - Identify significantly different links that form a connected structure instead of individual links.

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Results.

Permutation test results from 100 strongest + MinST networks.

	ASD > NT i.e. hyperconnected	ASD < NT hypoconnected
Degree *	Right superior middle frontal gyrus, left post central gyrus, right striatum	Right inferior temporal gyrus, left amygdala, left striatum
Clustering coefficient (Global) *	No significant difference between groups	No significant difference between groups
Clustering coefficient (Local) *	Precentral gyri (L+R), left paracentral lobule	Left superior and middle frontal gyri, inferior temporal gyri (L+R), right inferior parietal lobe, left precuneus, left cingulate gyrus
Average shortest path length *	No significant difference between groups	No significant difference between groups

* 20 000 permutations, FDR correction (BH) and alpha 0.05.

Table doesn't include all significant nodes. Full list is available at the end of presentation

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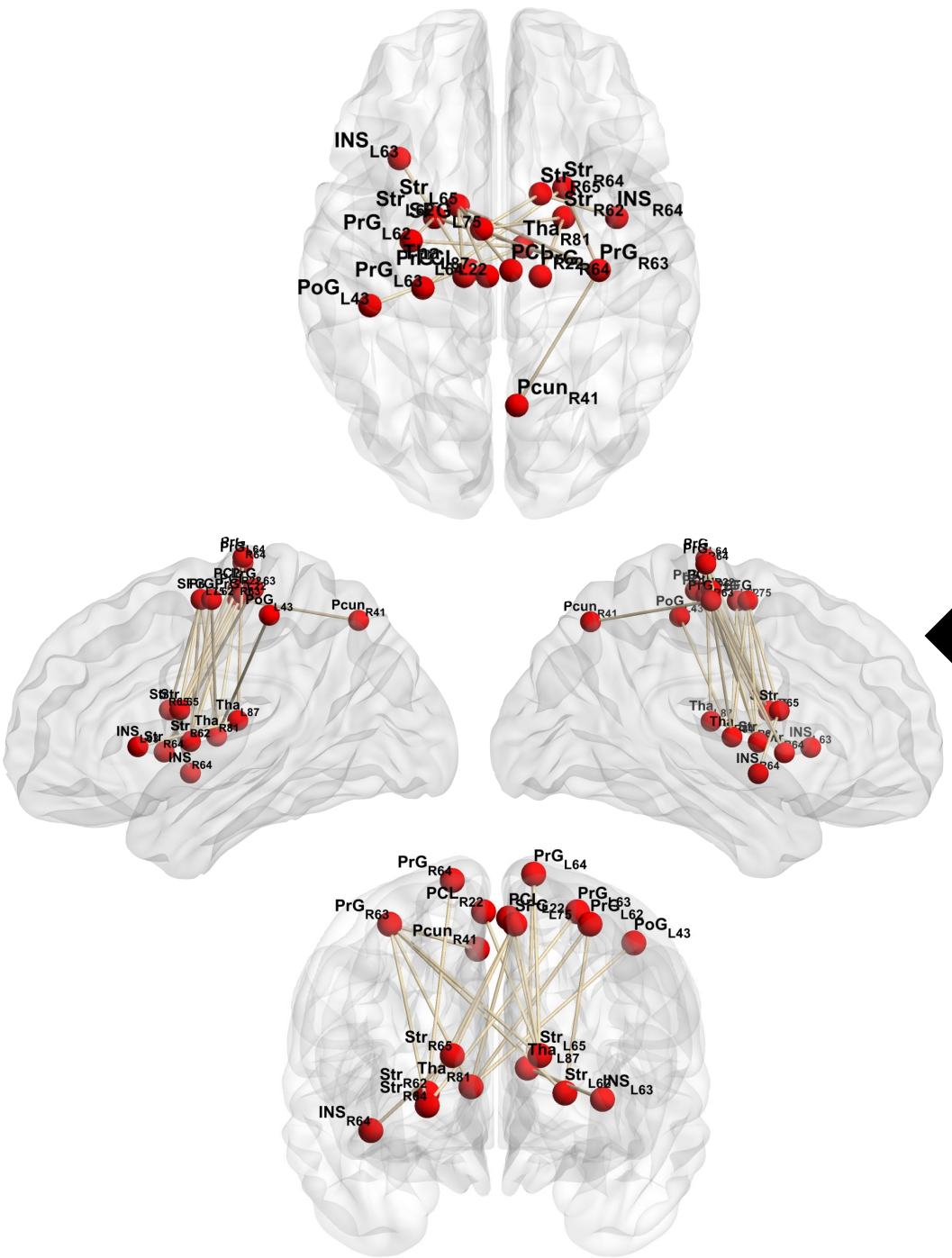

- Network based statistics (NBS): 5000 iterations, threshold = 3.5.
- NBS uses unthresholded adjacency matrices.
- The figure on the left represents ASD>NT, i.e., the hyperconnectivity.
- The test shows thalamocortical hyperconnectivity, similar to the previous study.

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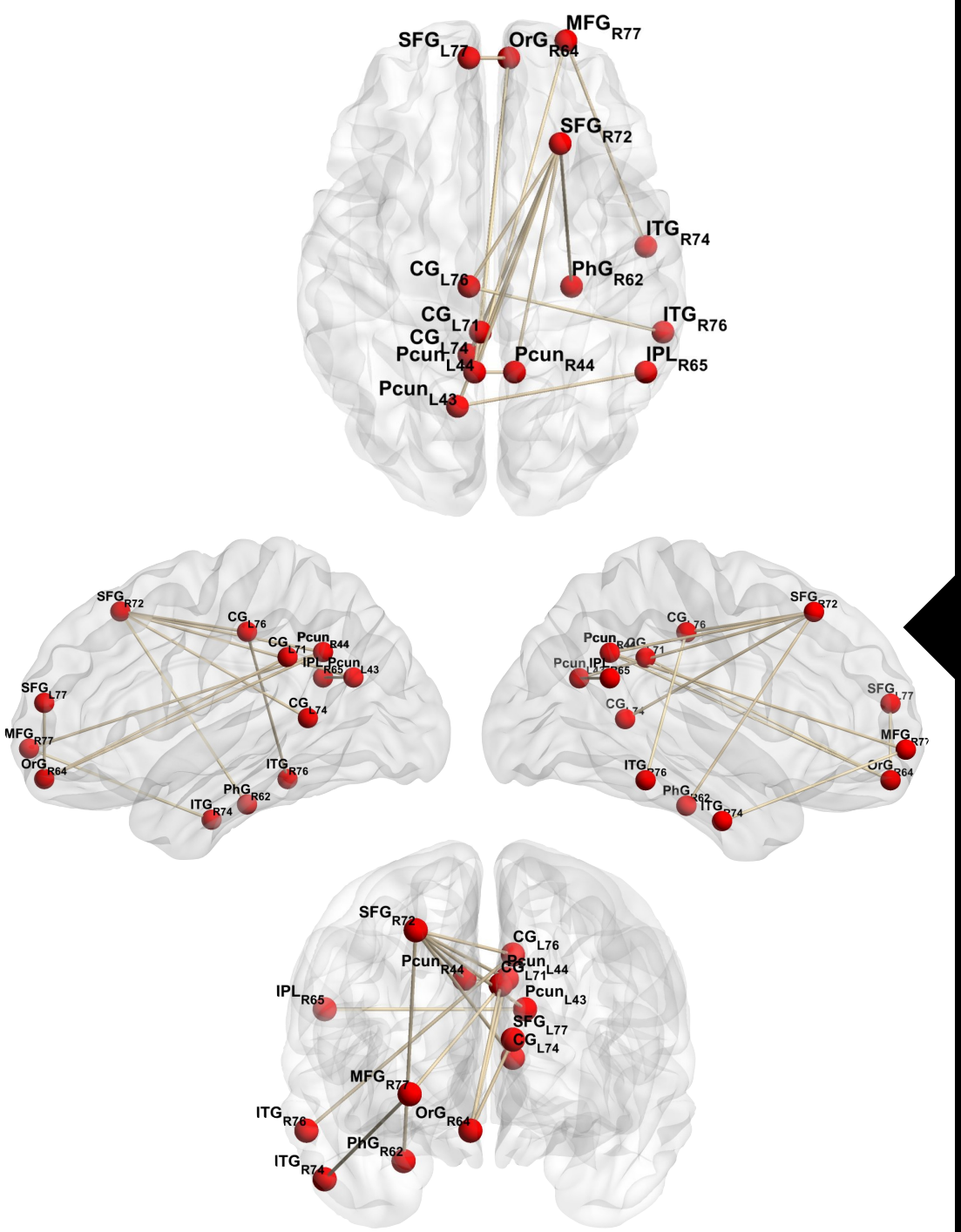

- Similar NBS test for ASD<NT, i.e., the hypoconnectivity.
- We see unilateral hypoconnectivity.
- Cingulate gyrus and precuneus nodes are highlighted in the test (edge to frontal lobe).

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Conclusion.

We found thalamocortical hyperconnectivity and unilateral hypoconnectivity.

- Hypoconnectivity result differs from previous studies with the same data set.
  - It could be due to different parcellation and regression.

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We learned how network analysis is done with real-life fMRI data.

- ASDs have network differences compared to NTs.
- How permutation tests can be used to assess the statistical significance of network metrics and how brain networks can be visualized.

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Hands-on Network Analysis

Appendix.

Appendix 1. Degree permutation results.

	ASD > NT i.e. hyperconnected		ASD < NT hypoconnected	
Degree. Node and p-values	SFG_R_7_4 0.02925	MFG_R_7_2 0.02605	MTG_R_4_3 0.0261	ITG_R_7_4 0.0476
	MFG_R_7_4 0.01435	MFG_R_7_6 0.01025	pSTS_R_2_2 0.02155	SPL_L_5_1 0.01885
	OrG_L_6_2 0.0166	STG_L_6_4 0.02505	SPL_L_5_2 0.00465	SPL_L_5_4 0.0325
	MTG_R_4_2 0.00935	PhG_L_6_4 0.01345	IPL_L_6_2 0.02865	IPL_L_6_5 0.01155
	IPL_L_6_4 0.04515	Pcun_L_4_2 0.008	Pcun_L_4_1 0.01645	PoG_R_4_3 0.0483
	PoG_L_4_2 0.03375	INS_L_6_3 0.0162	INS_R_6_2 0.0256	Cun_R_5_2 0.03325
	INS_R_6_3 0.00485	INS_R_6_4 0.0253	Cun_R_5_4 0.03055	sOcG_R_2_2 0.01235
	INS_R_6_6 0.0374	CG_L_7_2 0.01725	Amyg_L_2_1 0.01305	Str_L_6_6 0.01445
	Cun_L_5_3 0.01685	OcG_L_4_2 0.00825		
	Str_R_6_2 0.00625	Str_R_6_6 0.01755		

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Appendix 2. Clustering coefficient permutation results.

	ASD > NT i.e. hyperconnected	ASD < NT hypoconnected
Clustering coefficient (Local). Node and p-values	SFG_L_7_3 0.0033 IFG_L_6_2 0.0498 PrG_L_6_1 0.01885 PrG_R_6_5 0.03215 PCL_L_2_1 0.0259 Tha_R_8_7 0.0 Tha_L_8_8 0.0 Tha_R_8_8 0.0	SFG_L_7_5 0.0291 OrG_R_6_1 0.04025 MTG_R_4_1 0.049 ITG_L_7_4 0.0344 PhG_L_6_4 0.03335 IPL_R_6_1 0.0174 PoG_L_4_3 0.03095 PoG_R_4_4 0.0446 CG_L_7_3 0.02795 CG_L_7_6 0.00815 Tha_R_8_4 0.0 Tha_R_8_7 0.0 MFG_L_7_7 0.0222 STG_R_6_4 0.01635 ITG_R_7_1 0.02445 PhG_L_6_3 0.00195 pSTS_R_2_2 0.0081 Pcun_L_4_1 0.03735 PoG_R_4_3 0.0275 INS_L_6_1 0.0 CG_R_7_3 0.0 Cun_R_5_1 0.0 Tha_R_8_6 0.0263 Tha_L_8_8 0.0 Tha_R_8_8 0.0

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Appendix 3. NBS permutation results.

	ASD > NT i.e. hyperconnected	ASD < NT hypoconnected
NBS links and test statistics.	PrG_R_6_3 to Pcun_R_4_1. Test stat: 4.07 PrG_L_6_2 to Str_L_6_2. Test stat: 3.59 PrG_R_6_3 to Str_L_6_2. Test stat: 3.52 SFG_L_7_5 to Str_R_6_2. Test stat: 3.66 PrG_R_6_4 to Str_R_6_2. Test stat: 4.70 PrG_L_6_3 to Str_R_6_4. Test stat: 4.16 PrG_R_6_3 to Str_R_6_4. Test stat: 3.81 SFG_L_7_5 to Str_L_6_5. Test stat: 3.81 PrG_R_6_3 to Str_L_6_5. Test stat: 3.83 PrG_L_6_4 to Str_L_6_5. Test stat: 3.82 PCL_L_2_2 to Str_L_6_5. Test stat: 3.69 PCL_R_2_2 to Str_L_6_5. Test stat: 3.89 SFG_L_7_5 to Str_R_6_5. Test stat: 4.14 INS_R_6_4 to Str_R_6_5. Test stat: 3.72 SFG_L_7_5 to Tha_R_8_1. Test stat: 4.28 PrG_L_6_2 to Tha_R_8_1. Test stat: 3.87 PrG_R_6_3 to Tha_R_8_1. Test stat: 3.51 PoG_L_4_3 to Tha_R_8_1. Test stat: 3.76	SFG_L_7_7 to OrG_R_6_4. Test stat: 3.74 MFG_R_7_7 to ITG_R_7_4. Test stat: 3.58 SFG_R_7_2 to PhG_R_6_2. Test stat: 4.28 SFG_R_7_2 to Pcun_L_4_3. Test stat: 3.97 IPL_R_6_5 to Pcun_L_4_3. Test stat: 3.93 SFG_R_7_2 to Pcun_L_4_4. Test stat: 3.68 MFG_R_7_7 to Pcun_L_4_4. Test stat: 3.52 OrG_R_6_4 to Pcun_L_4_4. Test stat: 4.92 SFG_R_7_2 to Pcun_R_4_4. Test stat: 4.39 Pcun_L_4_4 to Pcun_R_4_4. Test stat: 3.52 OrG_R_6_4 to CG_L_7_1. Test stat: 3.54 SFG_R_7_2 to CG_L_7_4. Test stat: 3.53 SFG_R_7_2 to CG_L_7_6. Test stat: 3.60 ITG_R_7_6 to CG_L_7_6. Test stat: 3.83

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