
“The hubs of the human connectome are generally implicated in the anatomy of brain disorders”

Crossley, Mechelli, Scott, Carletti, Fox, McGuire, Bullmore **(2013)**

Statistical Connectomics
16 April 2015

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Opportunity

- Certain diseases → Certain hubs
- Hubs topologically valuable and biologically costly
- Hubs appear to be conserved across species

Challenge

- Constructing two networks based on DTI and functional studies from healthy subjects, and comparing them with disease studies.
- Gathering data from studies done on different diseases and performing statistical analysis on it. Normalize the data so that they were comparable (in sample size, accuracy, etc)

Action: Steps

1. DTI network (structural)
2. Test resilience of network to simulated attack
3. Meta-analysis: general lesion map
4. Map DTI hubs to lesion locations
5. Repeat for fMRI task-based network
(functional)

Step 1 Action: DTI

- Nodes: 401 regions
- Edges: Streamlines
- $n = 56$
- Voxel = $1.875 \times 1.875 \times 2.5 \text{ mm}^3$
- Going from subject to group network

Step 1 Graph attributes

Calculated:

- Degree
- Betweenness centrality
- Global efficiency
- Rich club coefficient
- Modularity
- Participation coefficient
- Connection distance (Euclidean space)

Step 2 Action: Testing *in silico*

- 1) Deleting nodes
 - a) Random attacks
 - b) Targeted attacks - Remove nodes in degree order
- 2) Deleting edges
 - a) Random attacks
 - b) Targeted attacks - Remove longest edges first

Step 2 Resolution

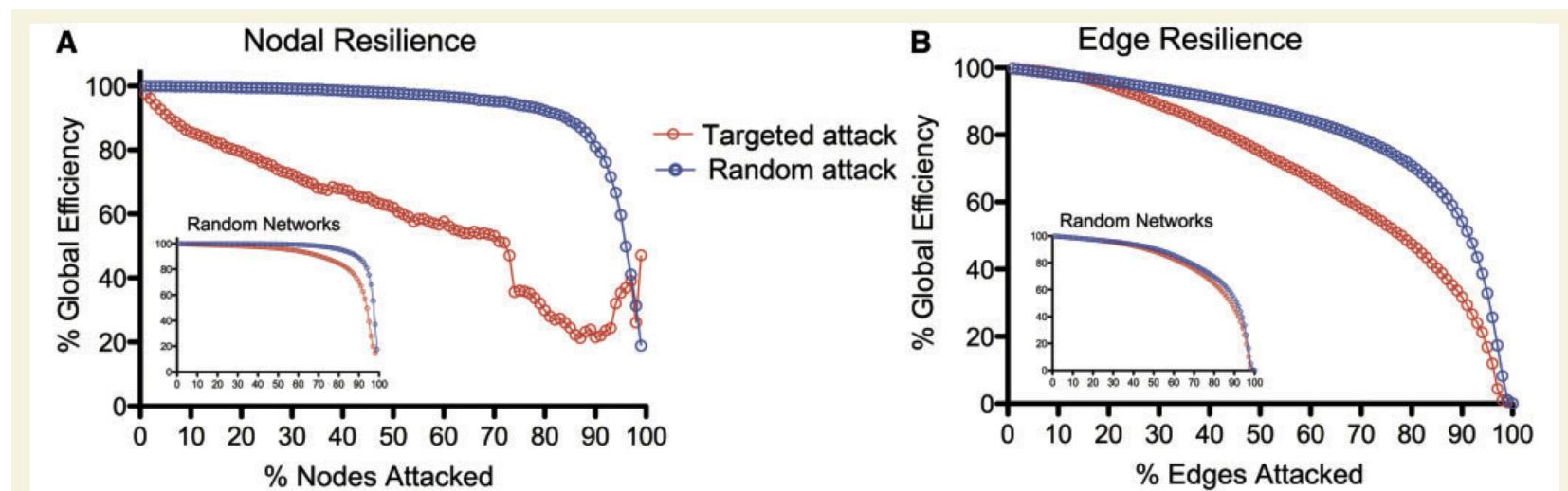


Figure 2 Computational attacks and the resilience of the DTI connectome. **(A)** Plot of global efficiency of the DTI network versus percentage of nodes deleted. When nodes are deleted randomly the efficiency of the network is approximately as resilient as a random (Erdős-Rényi) graph (*inset*); when high degree nodes are targeted (deleted in order of decreasing degree) the efficiency of the network degrades more rapidly than a random graph. **(B)** Plot of global efficiency of the DTI network versus percentage of edges deleted. The efficiency of the DTI network degrades faster than a random graph when the longer distance edges are targeted (deleted in order of decreasing connection distance).

Step 3 Action: Meta-analysis

- 26 disorders were studied
- Structural MRI studies that reported significant grey matter volume or density difference
- Anatomical likelihood estimation (ALE) to find locations of lesions averaged across a group of studies
- Maps obtained:
 - Per disorder
 - Overall - across disorder

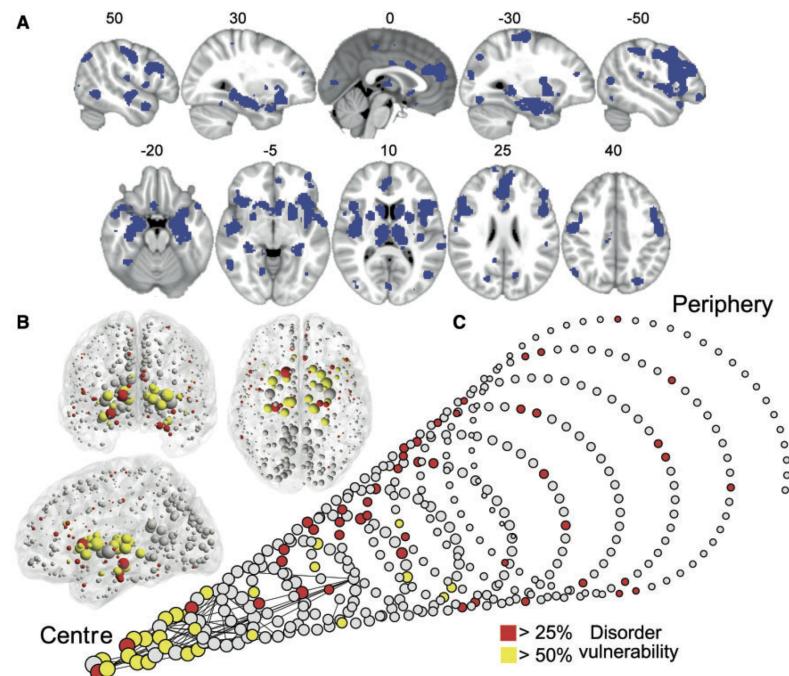
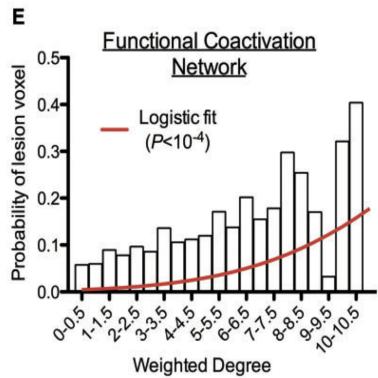
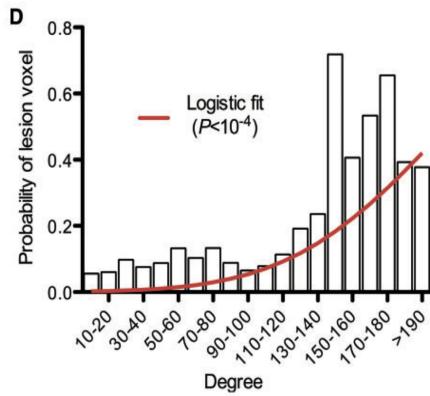
Step 4 Action: Relate hubs to lesion maps

- Define voxel in lesion map
 - Degree: mapped from respective DTI network regional node (out of 401)
 - Label (binary) - lesion or non-lesion
- Do logistic regression to relate binary label of each voxel to degree
 - Permutation testing - scramble degree labels of nodes and redo logistic regression- compare logistic regression coefficients for each voxel
- Compute difference between median degree of lesion voxel vs. non-lesion voxel
 - For each disorder (take subsets of the same size of studies of that disorder, create a lesion map each time, and repeat calculation)

Step 5 Action: Repeat for functional network

- 1641 fMRI task-based studies on healthy people
- Nodes: 638 similar-sized regions
- Edges: Based on Jaccard Index for each pair of regions
 - $\# \text{ studies in which both regions were activated} / \# \text{ studies in which at least 1 was activated}$

Steps 4 & 5 Resolution



Step 4 Resolution

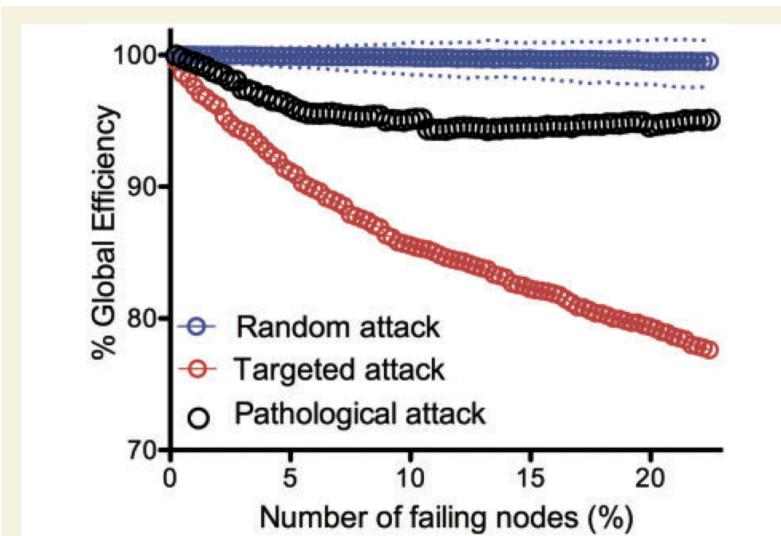
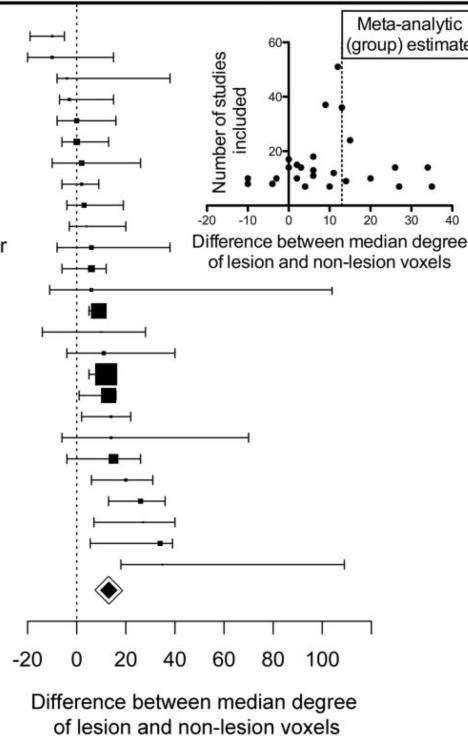


Figure 4 Modelling pathological attack on the connectome. Plot of the global efficiency of the DTI network versus percentage of nodes deleted. Note that the global efficiency deteriorates significantly faster in pathological attacks compared to random attack, but not to the extent of targeted attacks on hubs.

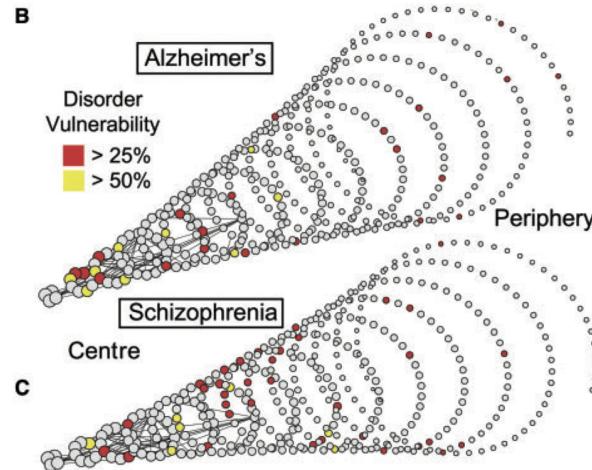
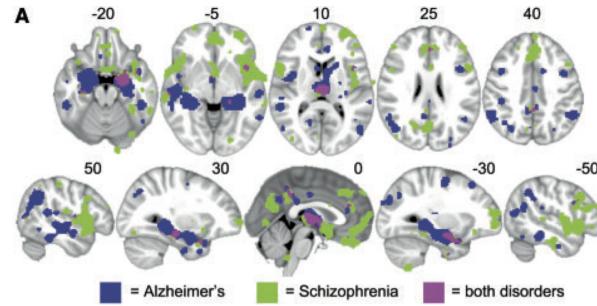
Step 5 Resolution

Brain Disorders

Amyotrophic lateral sclerosis
Dystonia
Developmental dyslexia
Anorexia nervosa
Obsessive-compulsive disorder
Parkinson's disease
Hereditary ataxia
Dementia in Parkinson's
Chronic pain
Panic disorder
Attention deficit hyperactivity disorder
Bipolar affective disorder
Multiple sclerosis
Frontotemporal dementia
Obstructive sleep apnea
Autism
Schizophrenia
Alzheimer's disease
Asperger syndrome
Huntington's disease
Depressive disorder
Right temporal lobe epilepsy
Post traumatic stress disorder
Progressive supranuclear palsy
Left temporal lobe epilepsy
Juvenile myoclonic epilepsy
Meta-analysis of all disorders



Step 5 Resolution



Future

- Examine the possibility that hubs are more vulnerable to attack
 - Look for genetic factors that change vulnerability of hubs
 - How the subset of hubs affected varies with disorder and what that could mean
 - Build a classifier/diagnosis tool to identify diseases based on affected hubs
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Global Efficiency

The average of the inverse of the shortest paths between each pair of nodes

Very efficient = small shortest paths = large inverses = large average :)

Not efficient = large shortest paths = small inverses = small average :)

Jaccard index

For each pair of regions, the number of studies activating both regions divided by the number of studies activating either one

Clustering Coefficient

The number of triangles around a node,
indicating the fraction of neighbors of a node
that are neighbors of each other

Rich club coefficient (at level k)

Take all the nodes of degree k or higher = n nodes

(n choose 2) total possible edges between them

Fraction of edges between them out of total

Participation Coefficient

A measure of the diversity of the intermodular connections of individual nodes

$$P_i = 1 - \sum \left(\frac{k_{is}}{k_i} \right)^2$$

Image Preprocessing ~DTI

- Correcting for Eddy currents and subject motion
- Normalization into standardized space using matrix rotation

Brain parcellation & map

- Talairach space → MNI space
- 401 similar regions based on Tzourio-Mazoyer

Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M.

Disorders used in meta-analysis

Table 1 Disorders included in the meta-analysis of grey matter lesions based on previously published voxel-based morphometry (VBM) studies

Disorder	Number of VBM studies included	Number of patients	Number of healthy controls
Attention deficit hyperactivity disorder	13	363	331
Amyotrophic lateral sclerosis	8	132	146
Anorexia nervosa	10	156	207
Asperger's syndrome	9	163	209
Autism (pervasive developmental disorder excluding Asperger's syndrome)	12	330	331
Bipolar affective disorder	18	479	630
Chronic pain	13	305	326
Dementia in Alzheimer's disease	36	765	1211
Dementia in Parkinson's disease	10	192	228
Depressive disorder	24	883	1015
Developmental dyslexia	8	121	122
Dystonia	10	219	244
Frontotemporal dementia	37	508	660
Hereditary ataxia	15	202	223
Huntington's disease	9	227	193
Juvenile myoclonic epilepsy	7	220	218
Multiple sclerosis	11	499	353
Obsessive-compulsive disorder	14	425	431
Obstructive sleep apnoea	7	177	268
Panic disorder	7	142	133
Parkinson's disease	17	515	411
Progressive supranuclear palsy	7	108	182
Post traumatic stress disorder	14	232	327
Schizophrenia	51	1925	2133
Temporal lobe epilepsy – left	14	339	597
Temporal lobe epilepsy – right	10	247	373
Total	392	9874	11502

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- Use Gaussian kernels with width=sample size used.
 - $P < 0.05$; cluster size threshold of 200mm³

Sources

- 1) Crossley, Nicolas; Mechelli, Andrea; Scott, Jessica; Carletti, Francesco; Fox, Peter T.; McGuire, Philip; Bullmore, Edward T. '**The hubs of the human connectome are generally implicated in the anatomy of brain disorders**'
- 2) <https://sites.google.com/site/bctnet/measures/list>
- 3) **Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain.** Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M.