Brain complexity

and disease

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Dr. Stefan Maas, BioS Lehigh U.
Brain networks
The adult brain weighs about 3 pounds.

The average number of neurons in the brain = 100 billion.

The average number of glial cells in the brain = 10-50 times the number of neurons.

more than 100,000 kilometers of inter-connections
Complexity of the Brain

100 billion neurons plus
>1 trillion glia cells connected by
100 Trillion synapses
in a single human brain
organized into exquisitely complex circuits...

responding to experience, drugs, disease, and injury...
Generation of Complexity

Areas generated = 2^n - 1 where n is the number of "things"
Complexity of the Brain

- Purkinje Cell
- Pyramidal Cell
- Small Gelatinosa Cell
- Spindle-Shaped Cell (Substantia Gelatinosa)
- Inferior Olivary Nucleus Neuron
Nerve Cell Communication

Synapse
Complexity of the Brain

The synapse typically has two parts:

A presynaptic structure containing packets of neurotransmitters

and a postsynaptic structure of the receiving neuron
Cerebral cortex

Information integration

cognition, thought, mood, emotion

Sensory input
acetylcholine
noepinephrine
serotonin
dopamine

Motor output

histamine
From Genes to Proteins

Genes contain instructions for making proteins.

Proteins act alone or in complexes to perform many cellular functions.

http://www.ornl.gov/hgmis/publicat/primer2001/
Gene splicing:
Removal of non-coding introns

Exon

Intron

mature splice product

PROTEIN
Principles of Alternative Splicing
RNA editing

transcription

A-to-I editing

splicing + translation

5’ A 3’

5’ A 3’

5’ I 3’

genomic DNA

pre-mRNA
### Mammalian substrates of A-to-I pre-mRNA editing

<table>
<thead>
<tr>
<th>Gene</th>
<th>codon</th>
<th>amino acid</th>
<th>editing [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>GluR-B</td>
<td>CAG/CIG</td>
<td>Q/R</td>
<td>100</td>
</tr>
<tr>
<td>GluR-B,-C,-D</td>
<td>AAG/AIG</td>
<td>R/G60-80</td>
<td></td>
</tr>
<tr>
<td>GluR-5,-6</td>
<td>CAG/CIG</td>
<td>Q/R</td>
<td>40-80</td>
</tr>
<tr>
<td>GluR-6</td>
<td>AUU/IUU</td>
<td>I/V</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>UAC/UIC</td>
<td>Y/C</td>
<td>80</td>
</tr>
<tr>
<td>5-HT_{2C}</td>
<td>AUA/IUA</td>
<td>I/V</td>
<td>40-90</td>
</tr>
<tr>
<td>Serotonin-receptor</td>
<td>AAU/AlU</td>
<td>N/S</td>
<td>35-40</td>
</tr>
<tr>
<td></td>
<td>AUU/IUU</td>
<td>I/V</td>
<td>45-75</td>
</tr>
</tbody>
</table>
Diversity through RNA editing

GluR-6 pre-mRNA

5' AUUAUU UACUAC CAGCAG 3'

unedited edited

GluR-6 N M1 M2 M3 C

I / V Y / C Q / R

M1 M2

h@lehig.edu
Diversity through RNA editing

GluR-6 pre-mRNA

M1
AUU IUU
M2
UAC UIC
M3
CAG CIG

I / V
Y / C
Q / R

GluR-6
N
M1
M2
C

I Y
I C
V Y
I Y
V C
I C
V Y
V C

unedited
10 %

unclassified
5 %

fully edited
65 %
Even more diversity

paralytic pre-mRNA

5' alternative splicing 3'

constitutive exon

alternative exon

1536 variants
Even more diversity

paralytic pre-mRNA

alternative splicing

RNA editing

1,032,192 variants
World Wide Web

Over 3 billion documents

ROBOT: collects all URL’s found in a document and follows them recursively

P(k) ~ k^\gamma

(a) Prevalence of neurological disorders

- Epilepsy: 2,000,000
- Stroke: 1,800,000
- Alzheimer’s disease: 3,000,000
- Parkinson’s disease and Huntington’s disease: 500,000
- Early developmental disorders (mental retardation, cerebral palsy, perinatal injuries): 750,000
- Head and spinal cord trauma: 1,000,000

*Biological Psychology 5e, Figure 1.7 (Part 1)*
(b) Incidence of psychiatric disorders

- Alcohol and drug abuse: 15,000,000
- Severe anxiety: 16,000,000
- Severe depression: 10,000,000
- Schizophrenia: 1,500,000

U.S. population: 19%
Schizophrenia
True or False?

1. Schizophrenia is a rare illness

2. Schizophrenia generally strikes older people

3. People with Schizophrenia have multiple or split personalities

4. More hospital beds are occupied by people with Schizophrenia than any other medical illness
Schizophrenia

- Mental illness
- One of the top ten causes of long term disability
- Currently ca. 1% of population affected across countries and cultures
- Same in developed and developing countries
- Incidence of 0.2-0.4 per 1000

=> Lifetime risk of 1% for women and men
Schizophrenia

- develops between ages 15 and 25 and mostly persists throughout the patient’s lifetime

- cause unknown
  
  => genetic factors

  => early environmental influences

  => social factors
Symptoms and Disease Progression

Three broad types of Symptoms:

- Positive (psychotic) Symptoms
- Negative (depressive) Symptoms
- Cognitive and Social Impairment
Symptoms and Disease Progression

▸ Positive (psychotic) Symptoms

▸ Occur last, after several years of onset
▸ Most apparent and often lead to first psychiatric contact, tend to be episodic

- Loss of contact with reality
- Delusions (false beliefs)
  
  *for example:* persecutory delusions, delusions of control, grandiose delusions and somatic delusions
- Hallucinations (auditory, visual, olfactory, tactile)
  
  Auditory hallucinations most common
Symptoms and Disease Progression

> **Negative (depressive) Symptoms**

> Occur first

> Less dramatic but more pervasive and fluctuate less over time

- Blunted affect
  - eg, immobile facial expression, monotonous voice tone

- Anhedonia (lack of pleasure)

- Apathy
  - diminished ability to initiate and follow through on plans

- Alogia
  - reduced quantity of speech
Symptoms and Disease Progression

- Cognitive and Social Impairment

  - Occur second

- Attention and Concentration deficits

- Problems with Learning and Memory

- Deficiency in executive Function
  
  abstract thinking, problem solving
## Genetic factor

<table>
<thead>
<tr>
<th>Genes shared</th>
<th>Relationship to person with schizophrenia</th>
<th>Risk of developing schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>Identical twins</td>
<td>48%</td>
</tr>
<tr>
<td>50%</td>
<td>Siblings</td>
<td>9%</td>
</tr>
<tr>
<td>25%</td>
<td>Children</td>
<td>13%</td>
</tr>
<tr>
<td>12.5%</td>
<td>Fraternal twins</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>General population</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>First cousins</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Uncles/Aunts</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Nephews/Nieces</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Grandchildren</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Half siblings</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Parents</td>
<td>6%</td>
</tr>
</tbody>
</table>

Genetic factors

Genetic transmission does not follow simple Mendelian single-gene inheritance patterns

- Multiple susceptibility genes, each with small effect and acting in concert with environmental factors

Several genes shown to be linked with schizophrenia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Populations studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRG1</td>
<td>8p12-p21</td>
<td>Icelandic</td>
</tr>
<tr>
<td>DTNBP1</td>
<td>6p22</td>
<td>Irish</td>
</tr>
<tr>
<td>G72</td>
<td>13q34</td>
<td>French Canadian, Russian</td>
</tr>
<tr>
<td>DAAO</td>
<td>12q24</td>
<td>French Canadian</td>
</tr>
<tr>
<td>RGS4</td>
<td>1q21-22</td>
<td>USA ×2, Indian</td>
</tr>
<tr>
<td>COMT</td>
<td>22q11</td>
<td>USA, Israel, Chinese</td>
</tr>
<tr>
<td>PRODH</td>
<td>22q11</td>
<td>USA</td>
</tr>
</tbody>
</table>
Environmental factors

**Biological:**
Prenatal events or birth complications
Infections, hypoxia, winter birth, maternal malnutrition or use of psychoactive drugs

**Psychosocial:**
Poverty and lower social class
Stressful environmental conditions

Urban versus rural background
Pathophysiology

- Enlargement of the ventricular system
- Accompanied by overall reduction in brain volume and cortical grey matter

Changes are not directly linked to illness progression
Pathophysiology

Is Schizophrenia a demyelinating disorder?
- Some symptoms (psychosis, cognitive impairments) are similar to MS symptoms
- Time of onset is similar

Is Schizophrenia a neurodevelopmental disorder?
- prevailing pathogenic model for Schizophrenia
- anatomical changes due to abnormal early brain development (visible before first episode)
- No sign of repair or degenerative processes (glial reactions, plaques)
- indications of defect in neuronal migration

Late onset related to processes during adolescence and early adulthood (excessive synaptic pruning?)
Therapy - Management
# Therapy - Management

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>SZ symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Neuroleptics, Amphetamine</td>
<td>Antagonists of D2 receptor, Increase dopamine</td>
<td>↓</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Phencyclidine, D-serine, D-cycloserine, glycine</td>
<td>Antagonist of NMDA receptor, Agonist of NMDA receptor</td>
<td>↑, ↓</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Atypical antipsychotics (clozapine)</td>
<td>Binding to 5-HT2 receptor</td>
<td>↓</td>
</tr>
</tbody>
</table>

Also: antidepressants, mood stabilizers, benzodiazepines

Combination therapy *(polypharmacy)* common
Therapy - Management

**Major problem:** non-compliance
ca. 50% (and higher soon after onset of disorder)

⇒ injectible depot
⇒ simplifications of regimen
⇒ direct delivery..
Therapy - Management

Early intervention

- prolonged untreated psychosis requires extended treatment
- Clinical symptoms worsen over the first several years
- worse prognosis after prolonged social isolation

Increased efforts to detect first-episode schizophrenia
Even better: before major symptoms appear
True or False?

1. Schizophrenia is a rare illness
   False: world-wide rate is 1:100

2. Schizophrenia generally strikes older people
   False: age of onset is 15-25

3. People with Schizophrenia have multiple or split personalities
   False: they are split from reality

4. More hospital beds are occupied by people with Schizophrenia than any other medical illness
   True: 8% of hospital beds