Brain complexity

and disease

September 24, 2010   Dr. Stefan Maas, BioS Lehigh U.
Sizing up Consciousness
NYT,  September 20, 2010
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

The adult brain weighs about 3 pounds.
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…
Areas generated = $2^n - 1$ where $n$ is the number of "things"
Complexity of the Brain
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

Sensory input

Motor output

Information integration
cognition, thought, mood, emotion

acetylcholine
norepinephrine
serotonin
dopamine
histamine
From Genes to Proteins

Genes contain instructions for making proteins.

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

Excitatory input

Neuromodulatory inputs

NE

ACh

DA

5-HT

Hist

β1

M1

D1

H2

5-HT2C

H1

Hist
Gene splicing:
Removal of non-coding introns

Exon

Intron

mature splice product

PROTEIN
Principles of Alternative Splicing
RNA editing

5' A 3'

transcription

5' A 3'

A-to-I editing

5' I 3'

splicing + translation

genomic DNA

pre-mRNA

Modified Regions
# 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/G</td>
<td>60-80</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$_2$C</td>
<td>AUA/IUA</td>
<td>I/V</td>
<td>40-90</td>
</tr>
<tr>
<td>Serotonin-receptor</td>
<td>AAU/AIU</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

GluR-6

5' 3'

M1 M2 M3

AUUAUU UACUAC CAGCAG

IUU IIUU UIC CCIIGG

M1 M2

I / V Y / C Q / R

unedited edited
Diversity through RNA editing

GluR-6 pre-mRNA

GluR-6

M1

M2

M3

AUU

IUU

I / V

CAG

UAC

UIC

Y / C

CIG

Q / R

N

M1

M2

M3

I Y

I C

V Y

I Y

V C

I C

V Y

V C

Q

Q

Q

R

Q

R

R

fully edited

unedited

10 %

5 %

5 %

10 %

5 %

65 %
Even more diversity

paralytic pre-mRNA

5’ alternative splicing 3’

constitutive exon
alternative exon

1 536 variants
Even more diversity

paralytic pre-mRNA

5’        3’

alternative splicing

RNA editing

1 032 192 variants
Engineered Networks

- **Nodes:** WWW documents
- **Links:** URL links
  - ROBOT collects all URL's found in a document and follows them recursively

\[ P(k) \sim k^{-\gamma} \]

- **Expected:**
  - \( P(k) \)
  - \(<k>\)

- **Found:**
  - \( P_{\text{exp}}(k) \)
  - \( k \)

Metabolic Network  

Protein Interactions
Internet-Map
(a) Prevalence of neurological disorders

- Alzheimer’s disease: 3,000,000
- Epilepsy: 2,000,000
- Stroke: 1,800,000
- 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
(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>12.5% 3rd-degree relatives</td>
<td>General population</td>
<td>1%</td>
</tr>
<tr>
<td>25% 2nd-degree relatives</td>
<td>First cousins</td>
<td>2%</td>
</tr>
<tr>
<td>50% 1st-degree relatives</td>
<td>Uncles/Aunts</td>
<td>2%</td>
</tr>
<tr>
<td>100%</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>
<tr>
<td></td>
<td>Siblings</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Fraternal twins</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Identical twins</td>
<td>48%</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 in synaptic cleft</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
Major problem: non-compliance
cia. 50% (and higher soon after onset of disorder)

⇒ injectible depot
⇒ simplifications of regimen
⇒ direct delivery..
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