Brain complexity ..................
............................... and disease

September 5, 2008  Dr. Stefan Maas, BioS Lehigh U.
Brain networks
Brain Trivia

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
Nerve Cell Communication

Synapse
The synapse typically has two parts:

A presynaptic structure containing packets of neuro-transmitters and a postsynaptic structure of the receiving neuron.
Information integration
cognition, thought,
mood, emotion

Sensory input

Motor output

Cerebral cortex

acetylcholine
norepinephrine
serotonin
dopamine
histamine
Glutamate

Excitatory input

Neuromodulatory inputs

NE

DA

Hist

SMAAS@lehigh.edu

Ca\(^{2+}\)

Ca\(^{2+}\)-dependent Kinases/phosphatases

Down-stream substrates

Gene expression

Short-term synaptic modification

Long-term synaptic modification

cAMP

PKA

IP3 + DG

PKC

β\(_1\)

D\(_1\)

M\(_1\)

H\(_2\)

H\(_1\)

5-HT

5-HT\(_{2C}\)

Hist

ACh

NE ACh 5-HT Hist

Hist
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/hgms/publicat/primer2001/
Genes code for Proteins with RNA as an intermediate
Glutamate
Excitatory input

Neuromodulatory inputs
NE
DA
Hist

D1
H1
H2
β1
M1
5-HT
5-HT2C
ACh
Hist

GluR
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
Adenosine converted to Inosine
- Interpreted as Guanosine
- Expand the proteome
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/AlG</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/IIU</td>
<td>I/V</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>UAC/IIIC</td>
<td>Y/C</td>
<td>80</td>
</tr>
<tr>
<td>5-HT$_{2C}$</td>
<td>AUA/IIUA</td>
<td>I/V 40-90</td>
<td></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/IIUU</td>
<td>I/V 45-75</td>
<td></td>
</tr>
</tbody>
</table>
Diversity through RNA editing

GluR-6 pre-mRNA

[Diagram showing regions M1, M2, and M3 with nucleotide sequences AUU, UAC, IUU, UIC, CAG, CIG, and transitions I/V, Y/C, Q/R indicated.]

unedited
edited
Diversity through RNA editing

GluR-6 pre-mRNA

M1

M2

M3

5’

I

V

Y

C

I

V

Y

C

Q

R

A

U

C

U

I

U

C

N

C

unedited

edited

unedited

10 %

} 5 %

} 5 %

} 10 %

} 5 %

fully edited 65 %
Even more diversity

paralytic pre-mRNA

1 536 variants

alternative splicing

constitutive exon
alternative exon
Even more diversity

-paralytic pre-mRNA

1,032,192 variants

alternative splicing

RNA editing

- constitutive exon
- alternative exon
- editing site
(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

- U.S. population: 19%
- Alcohol and drug abuse: 15,000,000
- Severe anxiety: 16,000,000
- Severe depression: 10,000,000
- Schizophrenia: 1,500,000
Q/R-site editing of glutamate receptor subunit GluR-B

mRNA

- UUU  AUG  CAG  CAA  GGA-

F  M  Q/R  Q  G

GluR-B

cytosol
Q/R-site editing of glutamate receptor subunit GluR-B

mRNA

-UUU AUG CAG CAA GGA-

F M Q/R Q G

GluR-B

cytosol

>99.9% R
RNA editing enzyme deficient mice

RNA editing enzyme deficient mice: Rescue by GluR-B point mutation

Glioblastoma multiforme (GBM)

http://www.thejohnphilpthompsonfoundation.org/GlioblastomaMultiforme_1_.jpg
Q/R site editing in normal human brain and gliomas

(Maas et al., 2001, PNAS 98, 14687-92)
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.

goal 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></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

[Cartoon image of a person looking at a map of a clinic with text: "Oak Tree Hill Schizophrenia Clinic" and the person saying, "You are here... Here... And here." ]
# 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</td>
<td>Antagonists of D2 receptor</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Amphetamine</td>
<td>Increase dopamine in synaptic cleft</td>
<td>↑</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Phencyclidine</td>
<td>Antagonist of NMDA receptor</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>D-serine, D-cycloserine, glycine</td>
<td>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
c. 50% (and higher soon after onset of disorder)

⇒ injectable 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
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