The Neurobiology of Schizophrenia

Dost Ongur, MD PhD
Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.
What is Psychosis?

Response

Representation

Reception

Language  Affect  Motor

S  A  V
Neural circuitry

M       S, A, V   Association

BG  Thalamus  MTL

DA  NE  5-HT  ACh

S, A, V

www.mghcme.org
The Reduced Neuropil Hypothesis

Selemon and Goldman-Rakic, 1999
GABAergic synapse

- **GABA** receptor
- **Cl⁻** transporter
  - **GABAₐ receptor**
  - **GABAₜ receptor**
  - **Modulators**: α: BZD, channel: Barbiturates, Ethanol

www.mghcme.org
Progressive Cortical Volume Loss

Thompson et al., 2001
Figure 2. Regions of differential gray matter change among participants who received cognitive enhancement therapy vs enriched supportive therapy. *P* values to the right of the slash reflect Hochberg’s correction. L indicates left; R, right; SE, standard error.
Thalamic Metabolism during Verbal Learning

Hazlett et al., 1999
Dopaminergic system

- N. accumbens
  - D3
- VTA
- SN
  - D1
  - D2
- Cortex
  - D1
  - D5
  - D4
- Caudate
  - D1
  - D2
- Putamen
  - D1
  - D2
- G. pallidus
- Thalamus
Dopaminergic synapse

D1, D5 receptors

D2, D3, D4 receptors

DAT
Striatal Dopamine Release

Laruelle et al., 1999

[p<0.001]

[p<0.001]

[p=0.3]
Glutamatergic synapse

Metabotropic receptors: mGluR$_{1-7}$

Ionotropic receptors:
- a) NMDA
- b) AMPA
- c) Kainate

Glutamate transporter

Na$^+$/Ca$^{++}$

Ca$^{++}$
NMDA receptor
<table>
<thead>
<tr>
<th>First author and year</th>
<th>Sample</th>
<th>Gene or region</th>
<th>Lowest p-values</th>
<th>OR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lencz 2007</td>
<td>178/144 (EA)</td>
<td>CSF2RA, SHOX</td>
<td>$3.7 \times 10^{-7}$</td>
<td>3.23</td>
<td>[68]</td>
</tr>
<tr>
<td>Sullivan 2008</td>
<td>738/733 (EA)</td>
<td>AGBL1</td>
<td>$1.71 \times 10^{-6}$</td>
<td>6.01</td>
<td>[125]</td>
</tr>
<tr>
<td>O’Donovan 2008</td>
<td>Discovery: 479/2937 (EA); follow up: 6829/9897 (EA)</td>
<td>ZNF804A</td>
<td>$1.61 \times 10^{-7}$</td>
<td>1.12</td>
<td>[97]</td>
</tr>
<tr>
<td>Need 2009</td>
<td>Discovery: 871/863 (EA); follow up: 1460/12,995 (EA)</td>
<td>ADAMTSL3</td>
<td>$1.35 \times 10^{-7}$</td>
<td>0.68</td>
<td>[93]</td>
</tr>
<tr>
<td>Purcell 2009 (ISC)</td>
<td>3322/3587 (EA)</td>
<td>MHC region$^a$</td>
<td>$9.5 \times 10^{-9}$</td>
<td>0.82</td>
<td>[107]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MYO18B</td>
<td>$3.4 \times 10^{-7}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stefansson 2009 (SGENE)</td>
<td>Discovery: 2663/13,498 (EA)</td>
<td>MHC region$^b$</td>
<td>$1.4 \times 10^{-12}$</td>
<td>1.16$^c$</td>
<td>[124]</td>
</tr>
<tr>
<td></td>
<td>Follow up: 4999/15,555 (EA)</td>
<td>NRGN$^b$</td>
<td>$2.4 \times 10^{-9}$</td>
<td>1.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCF4$^b$</td>
<td>$4.1 \times 10^{-9}$</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>Shi 2009 (MGS)</td>
<td>2681/2653 (EA)</td>
<td>MHC region$^a$</td>
<td>$9.5 \times 10^{-9}$</td>
<td>0.88</td>
<td>[118]</td>
</tr>
<tr>
<td></td>
<td>1286/973 (AA)</td>
<td>CENTG2 (in EA only)</td>
<td>$4.59 \times 10^{-7}$</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ERBB4 (in AA only)</td>
<td>$2.14 \times 10^{-6}$</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Combined analysis of ISC, SGENE, and MGS GWAS.

$^b$ Combined analysis of ISC, SGENE (including SGENE follow up samples) and MGS.

$^c$ OR is for common allele of the associated SNP, which is different from that in ISC and MGS.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Assay platform</th>
<th>Major findings</th>
<th>CNVs in case/control (interval in Mb and longest interval indicated; NA = data not available)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirov 2008</td>
<td>93 SZ trios</td>
<td>Array CGH</td>
<td>Two CNVs likely to be pathogenic</td>
<td>1q21.1 NA</td>
<td>[62]</td>
</tr>
<tr>
<td>Walsh 2008</td>
<td>150 cases/268 controls; 92 childhood onset SZ cases</td>
<td>Array CGH</td>
<td>Rare CNVs in 15% cases vs. 5% controls</td>
<td>1q21.1 1 del (51.14–51.32)</td>
<td>[139]</td>
</tr>
<tr>
<td>Xu 2008</td>
<td>359 SZ trios as screening sample; 152 cases/159 controls</td>
<td>Affy 5.0</td>
<td>In sporadic cases, frequency of rare de novo CNVs was 10% vs. 1.3% in controls</td>
<td>10 del (144.94–146.29)</td>
<td>[150]</td>
</tr>
<tr>
<td>Stefansson 2008</td>
<td>1433 cases/33,250 controls; 3 CNVs (1q11.1, 15q11.2 and 15q13.3) were followed up in 3285 cases/7951 controls</td>
<td>Varies</td>
<td>Three rare CNVs (1q11.1, 15q11.2, and 15q13.3) showed nominal association</td>
<td>11/8 del (144.94–146.29)</td>
<td>[123]</td>
</tr>
<tr>
<td>ISC 2008</td>
<td>3391 cases/3181 controls</td>
<td>Affy 5.0/6.0</td>
<td>Rare (&lt;1%) and large CNVs (&gt;100 kb) are enriched in cases (1.15-fold); 3 regions (1q11.1, 15q13.2, and 22q11.21) showed significant association</td>
<td>10/1 del (143.72–146.95) 5/6 del (50.8–51.50) 26/11 del (20.3–20.8) 9/0 del (28.0–31.0) 5/1 del (29.5–30.1)</td>
<td>[52]</td>
</tr>
<tr>
<td>Kirov 2009</td>
<td>471 cases/2792 controls</td>
<td>Affy 500K</td>
<td>Large CNVs (&gt;1 Mb) were 2.26 times over-represented in cases</td>
<td>0/2 del (144.9–146.3) 1/3 del (20.3–20.8)</td>
<td>[61]</td>
</tr>
<tr>
<td>Need 2009</td>
<td>1013 cases/1084 controls</td>
<td>HumanHap300, 550, or 610</td>
<td>Large CNVs (&gt;2 Mb) are enriched in cases. Summary frequency of implicated CNV (case vs. control)</td>
<td>1/0 del (144.1–146.3) 0.23% vs. 0.02% (del) 0.17% vs. 0.03% (del) 0.65% vs. 0.22% (del) 0.18% vs. 0.02% (del) 0.19% vs. 0.003% (dup)</td>
<td>[93]</td>
</tr>
</tbody>
</table>
Neurobiology of Schizophrenia

1) Multiple subtle abnormalities in most brain regions and chemical systems
2) No single lesion responsible for pathophysiology
3) Genetics points to neurodevelopment and synaptic plasticity
4) Deeper insights likely to come from “meta” level abnormalities in brain plasticity, connectivity, and information processing
Genetic predisposition

→

Early environmental insults

Neurodevelopmental brain abnormalities (schizotaxia): neurocognitive and social dysfunction

→

Later environmental insults

Prodrome and onset of psychosis (schizophrenia)

→

Toxic effects of psychosis

Neurodegeneration and chronic schizophrenia

Tsuang et al, 2001
Clinical Neuroscience in Mood Disorders

Dost Öngür, M.D., Ph.D.
Relevant Issues

• Episodic course
  – Symptoms not continuous following onset
  – Certain but not all abnormalities found in euthymia
  – Effects of the environment

• Variable presentation
  – Manic vs. Depressive episodes
  – “It is almost as if mania and melancholia are part of the same disease” – Arateus the Cappadocian
A Framework

• A condition that can be triggered by environmental events or endogeneously
  – Only in people with a vulnerability
• Once triggered, becomes an episode
  – Relatively stereotyped features but clear subtypes
• Typically self-limiting and episode ends once it has run its course
  – But vulnerability remains or is amplified
Phillips et al, 2003
Schultz, 2004

(a) Cereal < apple

(b) Apple < raisin
Fig. 3: Glutamatergic neurotransmission

Cell bodies:
- Cortex
- Thalamus
- Hippocampus
- Cerebellum
- Spinal chord

Glutamine → Glutaminase → Glutamate

(2) = Metabotropic receptors:
- mGluR,7

(1) = Ionotropic receptor
- a) NMDA
  - Modulators:
    - Glycine (+)
    - D-cycloserine (+)
    - PCP (-)
- b) AMPA
- c) Kainate

(3) = Glutamate transporter

Na⁺/Ca²⁺

Nucleus

adapted from Stephan Heckers, MD
The case of ketamine

Zarate et al 2010
Circadian Rhythm abnormalities in Bipolar Disorder
Evidence for circadian rhythm abnormalities

- Abnormal sleep and other circadian behaviors
- Seasonal pattern of episodes
- Induction of mania with sleep deprivation/travel across time zones
- Polymorphisms in genes controlling the biological pacemaker (*Clock* and related genes)
- Effect of sleep deprivation, phototherapy and sleep-entrainment
Table 2. Time to First Affective Episode in the Maintenance Phase as a Function of Acute Treatment Assignment: Survival Model After Stepwise Selection Procedure*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Parameter Estimate ± SE</th>
<th>Hazard Ratio</th>
<th>z</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute-phase IPSRT</td>
<td>-1.99 ± 0.42</td>
<td>0.34</td>
<td>-2.58</td>
<td>.01</td>
</tr>
<tr>
<td>Acute-phase IPSRT; anxiety disorder</td>
<td>1.72 ± 0.62</td>
<td>5.61</td>
<td>2.76</td>
<td>.006</td>
</tr>
<tr>
<td>IOM; anxiety disorder</td>
<td>0.36 ± 0.84</td>
<td>1.06</td>
<td>0.09</td>
<td>.93</td>
</tr>
<tr>
<td>Acute-phase IPSRT: inactive medical comorbidities</td>
<td>0.33 ± 0.13</td>
<td>1.39</td>
<td>2.62</td>
<td>.009</td>
</tr>
<tr>
<td>IOM: inactive medical comorbidities</td>
<td>-0.18 ± 0.12</td>
<td>0.84</td>
<td>-1.38</td>
<td>.13</td>
</tr>
<tr>
<td>Active medical comorbidities</td>
<td>0.11 ± 0.07</td>
<td>1.12</td>
<td>1.36</td>
<td>.10</td>
</tr>
<tr>
<td>Married</td>
<td>-1.40 ± 0.30</td>
<td>0.25</td>
<td>-3.68</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Index episode manic</td>
<td>0.34 ± 0.35</td>
<td>1.40</td>
<td>0.95</td>
<td>.34</td>
</tr>
<tr>
<td>Index episode mixed</td>
<td>1.14 ± 0.38</td>
<td>3.11</td>
<td>3.02</td>
<td>.003</td>
</tr>
</tbody>
</table>

Frank et al, 2005
per 1 peaks in early AM

per 2 peaks in afternoon

per 3

bmal 1

clock

Gene expression

High

Low

Midnight

Noon

10pm

NIGHT

SUBJECTIVE DAY

NIGHT

Bunney and Bunney, 2000
Clock mutant Mice

- Mutation in CLOCK generates a dominant-negative protein
- CLOCK expression is not cyclical, not restricted to suprachiasmatic nucleus
  - Mutant mice are hyperactive
    - At baseline
    - In response to novelty
    - Hypersensitive to cocaine
Clock mutant mice are more sensitive to reward

Roybal et al, 2007
Clock mutant mice show a less depressive-like phenotype

FST    LH    open field    elev maze    latency to feed

Roybal et al, 2007
Lithium reverses abnormalities in *Clock* mutant mice

Roybal et al, 2007
Clock mutant mice

• *Clock* mutant mice display increased cell firing and bursting in the VTA

• Viral-mediated gene transfer of functional CLOCK into the VTA
  – Hyperactivity and open-field abnormalities normalized
Antidepressants
• The mechanism of action of antidepressants is:
  – Upregulation of neurogenesis in the hippocampus?
Santarelli et al, 2003
Santarelli et al, 2003
Mood Stabilizers
The mechanism of action of mood stabilizers is:

- Modulation of intracellular signalling pathways to enhance cell survival and plasticity?
Figure 4. N-Acetyl-aspartate (NAA) increases on a regional basis (left); NAA increase positively correlates with percent voxel gray matter content (right). -■-, occipital; -●-, temporal; -▲-, frontal; -♦-, parietal.
Conclusions

• Etiology is elusive
  – Multiple intersecting factors of variable strength

• “Complex systems break in complex ways”

• Instead of searching for “the lesion”
  – Look for mechanisms to harness
    • Circadian rhythms
  – Think outside the box
    • Omega-3 FAs, inositol
    • Statins, Oral hypoglycemics
    • Ketamine