Biology of Psychopathology:

Biological perspectives on schizophrenia

1 May 2007

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What is *schizophrenia?*

- A clinical syndrome defined by a cluster of characteristic signs/symptoms
  - "Positive"
  - "Negative"
- No diagnostic test or biological marker
- Generally considered to be chronic and causing significant impairment

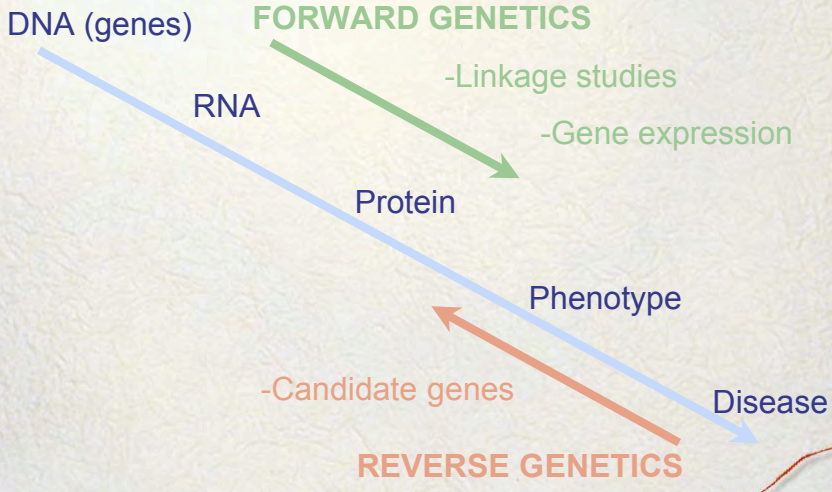
Brief history of schizophrenia

- 1800's - Descriptive reports. First characterized as a specific family of disorders (Kraeplin, Bleuler, Schneider)
- 1950's - efficacy of "neuroleptics". Discovery of D2 blockade by chlorpromazine (limbic and cortical effects). Induction of psychosis by amphetamine (D2 agonist).[Carlsson - 2000 Nobel; Delay and Deniker]
- 1970's/80's - efficacy of 'atypical' neuroleptics such as clozapine. Role of 5HT2 in negative symptoms.
- 1980's - characterization of chromosomal linkages, candidate genes, cognitive/electrophysiologic markers, etc.

Biological approaches:

- Neurotransmitters (based on medications)
- Linkage genetics
- Reverse genetics (candidate genes)
- Neuroanatomic/imaging
- Histology

Approaches to Understanding Biology of Disease



Neurotransmitters

Neurotransmitter	Drug	Mechanism of action	SZ symptom	Ref.
Dopamine	Neuroleptics	Antagonists of D2 receptor	↓	
	Amphetamine	Increase dopamine in synaptic cleft	↑	(2–4)
Glutamate	Phencyclidine	Antagonist of NMDA receptor	↑	(6)
	D-serine, D-cycloserine, glycine	Agonist of NMDA receptor	↓	(8, 9)
Serotonin	Atypical antipsychotics (clozapine)	Binding to 5-HT2 receptor	↓	(5)
	LSD		↑	
GABA	Benzodiazepines, gabapentin, anticonvulsants.			
Acetylcholine	Nicotine. Memory, etc.			

Sawa & Snyder; Table 1

GABA and Glu in Schizophrenia

- Decreased GABA neurotransmission in schizophrenia
- Genes in GABA and Glu system abnormal in some studies of schiz
- Specific subsets (PV+) of GABA neurons impaired.
- Glu antagonist models of psychosis
- Glu neurons activate GABA neurons (Glu antagonism decreases GABA chandelier cell output)

"The difficulty in designing anti-schizophrenia drugs stems from our ignorance as to the molecular causes of the disease and the absence of reliable animal models"

Sawa and Snyder

Heredity of Schizophrenia

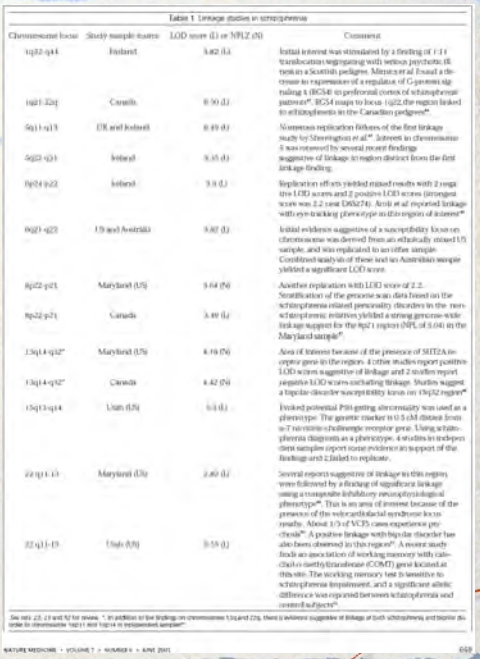
Affected Relative:	Relative Risk
None	1%
First degree relative	5-15%
Second degree relative	2-6%
Dizygotic twin	17%
Both parents	46%
Monozygotic twin	48%

Genetics

- Polygenetic disorder
- No single polymorphism in all cases
- “Stress diathesis” (combination of genetics and life events)
- Numerous implicated loci
- Growing number of candidate genes
  - COMT (Met form - 25% activity of Val form)
  - DISC-1
  - Neuregulin 1/ErbB
  - Reelin
  - Others

Chromosome Linkages

- Numerous chromosomes
- Some with identified target genes
- Varied strength



Candidate Genes

Genetics			Affected systems	Ref.
Method	Chromosomal locus	Candidate gene		
Linkage studies	1q21-22, 1q32-42, 6p24, 8p21, 10p14, 13q32, 18p11, 22q11-13	None		(*20–24*)
Chromosomal abnormalities	22q11 deletion (22qDS)	*COMT*	Dopamine; working memory	(*25–28*)
	Balanced translocation	*DISC-1*		(*29*)
Association studies		*5HT2A*	Serotonin	(*31, 32*)
Microarray technology		Synapsin II, NSF	Synaptic vesicle dynamics	(*33*)

- Neuregulin/Erb, DISC-1, dysbindin, Reelin
- BDNF/TrkB, IGF-1
- GABRA; GAD67; GAT-1 - GABA system
- Receptors (D1; a7 nicotinic; mGluR5; 5HT2A)
- Others (myelin related genes)

Sawa & Snyder; Table 2

COMT

- Catechol-O-Methyl-Transferase
- Dopamine metabolism
- Val-Met
  polymorphism
- Functional effect
  - Cognition
  - Other

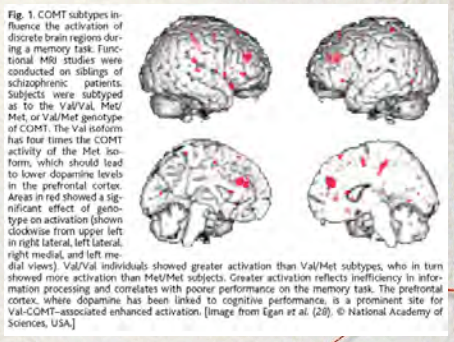


Fig. 1. COMT subtypes influence the activation of discrete brain regions during a memory task. Functional MRI studies were conducted on siblings of schizophrenic patients. Subjects were subtyped as to the Val/Val, Met/Met, or Val/Met genotype of COMT. The Val isoform has four times the COMT activity of the Met isoform, which should lead to lower dopamine levels in the prefrontal cortex. Areas in red showed a significant effect of genotype on activation (shown clockwise from upper left in right lateral, left lateral, right medial, and left medial views). Val/Val individuals showed greater activation than Val/Met subtypes, who in turn showed more activation than Met/Met subjects. Greater activation reflects inefficiency in information processing and correlates with poorer performance on the memory task. The prefrontal cortex, where dopamine has been linked to cognitive performance, is a prominent site for Val-COMT–associated enhanced activation. [Image from Egan et al. (20). © National Academy of Sciences, USA.]

Sawa & Snyder; Figure 1

Neuregulin-1

- Extracellular growth factor
- Signals through erb-B tyrosine kinase receptors
- Direct role as intracellular transcription factor?
- Erb-B assoc with NMDA receptors (plasticity role?)
- Also associated with BDNF function
- Association with cell migration. (COMT inhibits)

Neuregulin-1

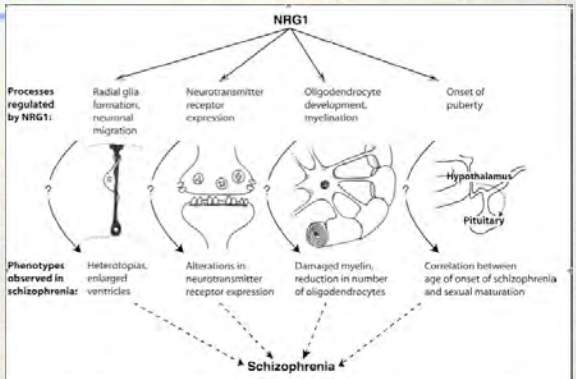


Figure 1 Potential relationships between NRG1 function and schizophrenia phenotypes. NRG1 has been implicated in cortical development by regulating radial glia morphology and neuronal migration, in synapse formation and function by regulating the expression of glutamate, GABA and ACh receptors, in myelination by regulating oligodendrocyte proliferation and differentiation, and in the control of the onset of puberty through the induction of LHRH release in the hypothalamus. All these developmental processes have been proposed to be altered or involved in schizophrenia. Thus, defects in NRG1 function can potentially contribute to the disease by altering one or more of these processes. The arrows with question marks indicate the current hypothetical nature of these possible links between NRG1 function and schizophrenia.

Neuregulin-1

- Role in regulating glutamate, acetylcholine, GABA receptor expression
- Associated with BDNF function
- Associated with oligodendrocyte maturation
- Role in radial glial cell migration
  - COMT inhibits
- Associated with PPI deficits

- Lower expression of NRG-1 or Erb-B in schizophrenia but no functional mutants identified

DISC1

- Identified in a linkage study
- Chromosome translocation segregating with schizophrenia
- Role in brain development
  - Migration, neurite outgrowth, neuron maturation
- Role in adult neuronal function
  - Cytoskeleton, synaptic transmission, plasticity
- Interacts with numerous other neural factors

Growth factors

- BDNF - development, plasticity
  - Growth factor signals through TrkB
  - Role in regulating GABA related genes
  - Mutation identified
  - Impaired working memory function in hippocampus (Egan, *Cell* 2003)
- IGF-1 - neurotransmitter function, metabolism

Anatomic studies

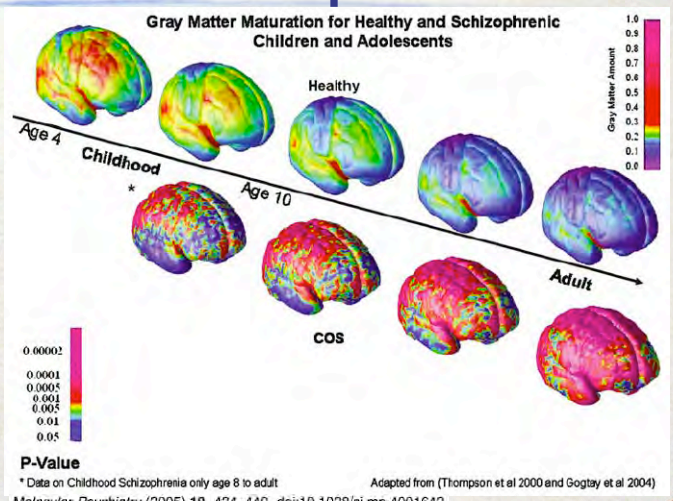
- Increased ventricle size?
- Reductions in specific brain regions:
  - PFC
  - Hippocampus
  - Thalamus
- Neurodevelopmental vs. neurodegenerative pattern of changes

Brain regions functionally implicated

- Prefrontal cortex
- Hippocampus
- Thalamic nuclei
- Auditory cortex
- White matter tracts

- Cognitive/executive fxn
- Working memory
- Sensory gating
- Hallucinations
- Hallucinations
- "Connectivity" - broad implications

Cortical Development in Schizophrenia



Molecular Psychiatry (2005) **10**, 434–449. doi:10.1038/sj.mp.4001642
Published online 8 February 2005

Histologic studies:

- Study of affected cell types and tissues
- Specific cell populations implicated
  - Glial cells (oligodendrocytes)
  - GABA neurons (chandelier cells)
  - Neurons (decreased cortical thickness)

Myelination

- Evidence for defective myelination
  - Developmental time course
  - Loss of oligodendrocytes
  - Structural loss of WM (DTI)
  - Primary or secondary effect?
- Relation to connectivity
- Myelin related genes

Alternate approaches?

- Endophenotypes

(or Intermediate Phenotypes)

- Maximize the chance of finding associated genes
- Minimize diagnostic uncertainty
- Improve reliability of measurements

Endophenotypes

- Identify an intermediate deficit
  - More quantifiable than psychiatric symptoms; “Closer” to genetic linkage
- Deficit must be heritable
- Must be ‘stable’
- Cosegregates with disorder
- Found more commonly in probands than general population

Endophenotypes - Caveats

- No *a priori* criteria for deciding if measure related to single gene
- Consistent measurement can be difficult
- May require a “challenge” to elicit
- May be attenuated by medication effects
- May not be specific to a single diagnosis/disorder

Endophenotypes - Benefits

- May reflect synaptic function more closely than disease symptoms
- Patients and relatives show a range of measures on endophenotypes - ideal for quantitative trait linkage analysis
- More homogenous study population, increasing the likelihood of identifying related genes.
- Ideal for designing animal models
- Can be used with both 'forward' and 'reverse' approaches

Types of Endophenotypes

- Cognitive
- Eye movements
- Electrophysiologic
- Imaging (structural or functional)
- Other?
  - Sleep EEG; synchrony; DTI (AJP Mar07)

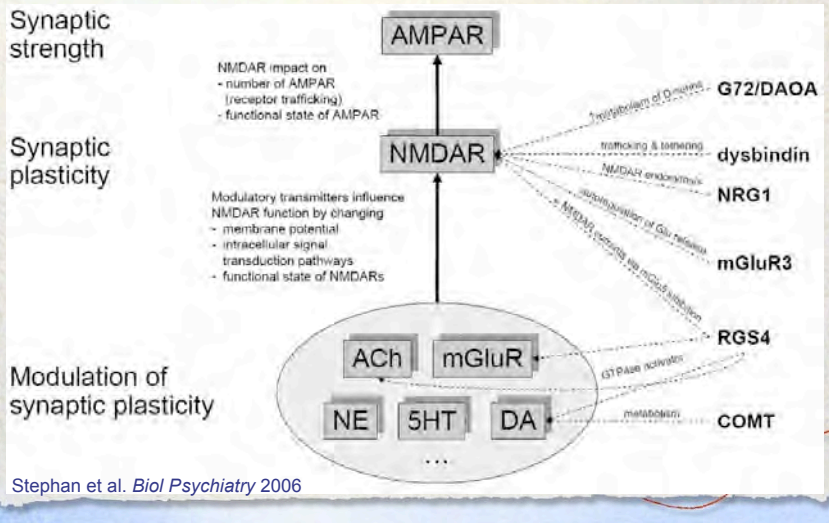
Pathophysiology of Schizophrenia

- Functional deficits
  - Plasticity
  - Connectivity
  - Developmental
    - cell migration
    - cortical development
    - myelination

Plasticity and Connectivity

- Synaptic plasticity
  - Cognitive and learning
  - Dendritic alterations
  - Candidate genes
- Functional connectivity
  - EEG data
  - fMRI and PET
- Structural connectivity
  - Histopathology
  - MRI - DTI

Plasticity and Connectivity



Stephan et al. *Biol Psychiatry* 2006

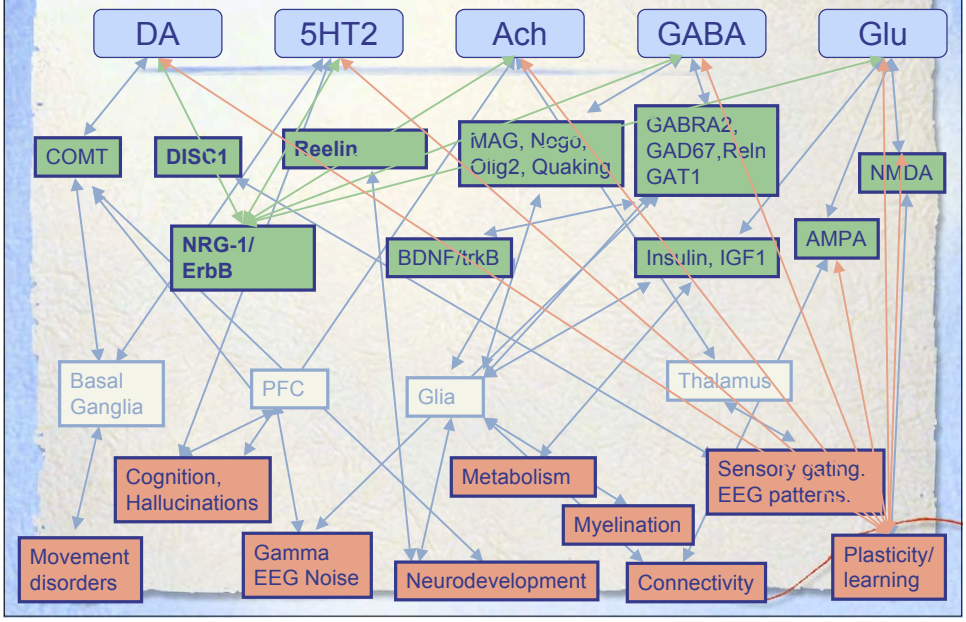
Neurodevelopment

- Neural migration (Reelin - “stop” signal for neural migration. Up to 50% decrease in schizophrenia. Especially involved w/ GABA neurons. COMT and Neuregulin also involved with migration.
- Myelination, oligodendrocytes
- Connectivity (age of onset, pruning)

Schizophrenia - summary

- Multiple neurotransmitters
- Multiple cell types
- Numerous 'candidate genes' and gene products with abnormal expression/regulation
- Related to developmental, cognitive, anatomic deficits/models
- Endophenotypes: stable cognitive, electrophysiologic, genetic patterns in subsets of affected individuals/relative

Neurobiology of Schizophrenia



Drug development targets:

- "Most promising targets for devolopment of a drug to treat cognitive impairments in schizophrenia"
  - Alpha-7 nicotinic receptor agonists
  - D1 receptor agonists
  - AMPA glutamatergic receptor agonists
  - Alpha-2 adrenergic receptor agonists
  - NMDA glutamatergic receptor agonists
  - Metabotropic glutamate receptor agonists
  - Glycine reuptake inhibitors
  - M1 muscarinic receptor agonists
  - GABA-A receptor selective agonists

Psychiatric News Jan 20,2006
www.matrics.ucla.edu

Novel therapeutic targets

- Kappa opioid receptor antagonists (Salvinorin; for anxiety/mood disorders)
- Calcium channel modulators
- Nicotinic agonists
- Muscarinic agents
- mGluR modulators
- GABA system modulators
  - Glycine transporter
  - Target specific GABA neuron populations

Current state of the neurobiology of schizophrenia

- Not as simple as previously hoped
- However…
  - Growing number of target genes, receptors, neurotransmitters
  - Multiple, comprehensive theories of neurobiology/etiology
  - More than ever, convergence of theories

Current state of the neurobiology of schizophrenia

- Schizophrenia likely a syndrome of multiple etiologies with common end points.
- Future generations of diagnostics and treatments will likely identify and target unique biological deficits in individuals

Thank you!

Please let me know if you have any questions or would like any additional references.

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