An Introduction to the Pharmacogenetics of Cognitive Improvement in Schizophrenia

14th Edmonton Schizophrenia Conference

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Neil Woodward has not received any financial support from the makers of any of the pharmaceutical products discussed in this presentation
Introduction

• Cognitive impairment is a fundamental feature of schizophrenia and an important determinant of functional outcome.

• The deficits in cognition are related, in part, to genetic vulnerability for the disorder.

• Cognition improves to a degree following treatment with some antipsychotic medications.

• Preliminary evidence suggests the degree of improvement may relate to genetics.
Objectives

1. Overview of Cognitive Impairment in Schizophrenia

2. Genetic Contributions to Cognitive Impairment in Schizophrenia

3. Cognitive Improvement with Antipsychotics in Schizophrenia and Genetics

4. Conclusions and Future Directions
Cognitive Impairment in Schizophrenia

- Impairment observed in several cognitive domains including attention, executive function, learning and memory
- The deficit is severe, on the order of 1 to 2 standard deviations below normal
- Deficits are observed early in the course of the illness and may predate the onset of florid psychotic symptoms
- Impairment does not progress: neurodevelopmental in origin
Neuropsychological Impairment in 1st Episode Schizophrenia

- Attention
- Verbal Ability
- Visuospatial Ability
- Memory
- Executive Function

Hoff et al., 92
Saykin et al., 94
Bilder et al., 00
The consequences of Cognitive Impairment

- Cognitive impairment is a strong predictor of outcome
- Cognition is more closely related to outcome than positive and possibly negative symptoms
- There are associations between specific cognitive skills and dimensions of outcome (Green et al., 1996; 2000).
Cerebral Basis of Cognitive Impairment in Schizophrenia

Insights from Functional neuroimaging

Abnormalities in distributed cortical-subcortical circuits

- Cognitive Dysmetria (Andreasen)
- Fronto-striatal circuitry (Buchsbaum, Pantelis)
- “Hypofrontality” and reduced “Cortical Efficiency” (Weinberger et al.)

- Alterations in cerebral function detected even when performance is normal at the behavioral level

Andreasen et al., 1999; Callicott et al., 2003
Cerebral Basis of Cognitive Impairment in Schizophrenia

The Mesocortical Dopamine (DA) System and Cognition

Mesocortical DA system originates in the VTA of the brainstem and projects to the PFC.

Essential for some executive cognitive functions.
Cerebral Basis of Cognitive Impairment in Schizophrenia

The Mesocortical DA System and Cognition in non-human primates

- working memory
- attentional set shifting

DA modulation of PFC neurophysiology

Control  Dopamine  DA antagonist

Errors to criterion

Criterion performance
Cerebral Basis of Cognitive Impairment in Schizophrenia

The Mesocortical DA System and Cognition: Neuroimaging Findings in Humans

- DA release during WM
  - Aalto et al., 2005

- DA agonists sharpen fMRI BOLD response during WM and attention tasks in patients with Parkinson’s Disease and controls
  - Mattay et al., 2000;
  - Mattay et al., 2002
  - Cools et al., 2002
Cerebral Basis of Cognitive Impairment in Schizophrenia

Mesocortical DA Dysfunction in Schizophrenia

- Post mortem evidence of reduced DA innervation of the PFC

D2 receptor up-regulation in schizophrenia revealed by PET

- DA agonists normalize cerebral activity and improve cognitive function in schizophrenia
  - e.g. Goldberg et al. 1988
  - e.g. Dolan et al., 1997
Cerebral Basis of Cognitive Impairment in Schizophrenia

Cerebral Structural Deficits in Schizophrenia

Grey matter volume loss in 1st episode schizophrenia

Lateral ventricle enlargement in schizophrenia

CONTROL

SCHIZOPHRENIA

Johnstone et al., 1976

Whitford et al., 2006
Genetic Contributions to Cognitive Impairment in Schizophrenia

- Schizophrenia is a heritable disorder—estimates range up to 80%.

- Distribution of risk in families indicates that schizophrenia is a polygenetic disorder and that environment plays a role in the manifestation of the illness.

Gottesman & Erlenmeyer-Kimling, 2001
Genetic Contributions to Cognitive Impairment in Schizophrenia

Cognitive impairment in schizophrenia is related to genetic vulnerability

Derived from Heinrichs & Zakzanis, 1998; Sitskoorn et al., 2004
Genetic Contributions to Cognitive Impairment in Schizophrenia

Alterations in cerebral function may also be heritable deficits

Unaffected siblings demonstrate abnormal PFC activity during working memory tasks

Unaffected siblings demonstrate less activity in PFC and parietal cortex during procedural learning despite demonstrating normal performance at the behavioral level

Woodward, Tibbo, & Purdon, Submitted
Genetic Contributions to Cognitive Impairment in Schizophrenia

Some aspects of abnormal cerebral structure in schizophrenia may relate to genetic vulnerability

A  Liability Correlation Map  B  Liability Significance Map  C  Liability Specificity Map

Cannon et al., 2002, PNAS
Genetic Contributions to Cognitive Impairment in Schizophrenia

- Multiple lines of evidence indicate that cognitive impairment in schizophrenia is related, in part, to genetic predisposition.

- Search for susceptibility genes has focused on genes related to DA function.

- The Catechol-O-Methyltransferase (COMT) gene has attracted considerable attention:
  - COMT is an enzyme involved in the metabolism of DA in the PFC.
  - Located on a chromosome linked to schizophrenia by linkage analysis.
  - Disrupted in Velo-cardio-facial Syndrome: a genetic disorder associated with high incidence of psychosis (15-30%).
Substitution of methionine (met) for valine (val) at codon 158 results in the transcription of a version of the COMT enzyme with less activity and presumably greater DA availability in PFC.

Lachman et al., 1996; Lotta et al., 1995; Chen et al., 2004
Genetic Contributions to Cognitive Impairment in Schizophrenia

• Mouse gene knockout studies and a preliminary imaging study in humans support the assumption that the val allele of the COMT SNP is associated with less PFC DA activity
  – Gene knockout (Gogos et al., 1998)
  – Human imaging (Meyer-Lindenberg et al., 2005)

• Given that greater endogenous PFC DA activity is associated with better PFC cognitive functions, then the met allele might be associated with better cognitive function

• Val allele may be over-transmitted to schizophrenia probands given that reduced PFC DA is associated with schizophrenia
  – Meta-analysis of family-based studies support this hypothesis, but the association is weak (Glatt et al., 2003; Munafo et al., 2005)
COMT Genotype and Cognitive Function

- Initial study by Egan et al. (2001) identified an association between COMT genotype, cognition, and risk for schizophrenia.

- The association between PFC cognitive function and COMT genotype has been replicated in unmedicated patients.

Woodward, Jayathilake, & Meltzer (in press)
COMT Genotype and Cerebral Neurophysiology

- COMT genotype is associated with PFC physiology
  - Met allele associated with more “efficient” PFC activity
- Val allele is associated with more PFC “noise” during working memory
- Differences observed in DLPFC, ant. Cingulate, and posterior regions
- Differences between genotype groups are observed even when performance and other variables (I.Q., age) are controlled for
Genetic Contributions to Cognitive Impairment in Schizophrenia

• Summary:
  – Cognitive impairment is a fundamental feature of schizophrenia that is also observed, to a lesser degree, in unaffected family members
  – Deficit reflects a fundamental alteration in cerebral function that may result, in part, from abnormal DA activity in the PFC
  – The COMT val158met SNP is related to PFC DA activity, cognitive function and neurophysiology, and is weakly associated with increased risk for schizophrenia

What does this have to do with cognitive improvement in schizophrenia?
Cognitive Improvement with Atypical Antipsychotics in Schizophrenia

• Antipsychotic drugs (APDs) include:
  – Typical APDs: Haloperidol, Chlorpromazine
  – Atypical APDs: Clozapine, Olanzapine, Risperidone, Quetiapine

• Typical APDs provide slight benefit to cognitive function (Goldberg et al., 2004; Woodward et al., in press)

• Atypical APDs improve cognitive function to a greater degree than typical APDs
Global Cognitive Change with Atypical APDs Compared to Typical APDs

Woodward et al., 2005
Cognitive Change with Atypical APDs Compared to Typical APDs

Woodward et al., 2005
Cognitive Improvement with Atypical Antipsychotics in Schizophrenia

- The pharmacological mechanism(s) underlying cognitive improvement with atypical APDs remains to be articulated

DA release in PFC with typical and atypical APDs

COMT inhibition potentiates this effect

Gessa et al., 2000

Tunbridge et al., 2005
Cognitive Improvement with Atypical Antipsychotics in Schizophrenia

- However, there is considerable variability in the degree of improvement observed on some cognitive measures.
Interactions Between COMT Genotype and Cognitive Change with APDs

• Preclinical evidence suggests that COMT activity and, hence, genotype, may interact with pharmacological effects of atypical antipsychotics

• COMT genotype may modulate the effect atypical antipsychotics have on cognitive functions
Interactions Between COMT Genotype and Cognitive Change with APDs

- First study by Weickert et al., 2004:
  - 20 subjects (5 val/val, 11 val/met, 4 met/met)
  - Tested during placebo medicated phases (counterbalanced design)
  - Patients received mostly atypical APDs
  - Met/met patients demonstrated greater improvement on n-back test of working memory

Weickert et al., 2004
Interactions Between COMT Genotype and Cognitive Change with APDs

• Second study by Bertolino et al., 2004:
  • 30 subjects (8 val/val, 17 val/met, 5 met/met)
  • Patients tested after 4 and 8 weeks Tx with olanzapine
  • Met/met patients demonstrated greater improvement on n-back test of working memory at 8 weeks

Bertolino et al., 2004
Interactions Between COMT Genotype and Cognitive Change with APDs

• Limitations of previous studies:
  – Very small sample sizes. 5 or fewer met homozygous subjects included in each of two previous studies
  – Limited cognitive battery administered. Analyses focused almost exclusively on a single working memory task
  – Variable medications given in one case
Experiment: Interactions between COMT genotype and cognitive change with clozapine

• **Methods**
  – 93 patients with schizophrenia (34 val/val, 37 val/met, 22 met/met)
  – All subjects completed a neuropsychological battery at baseline, and again after 6 weeks, and 6 months of clozapine
    • Working memory
    • Executive function
    • Verbal learning and memory
    • Processing speed
    • Verbal Fluency
  – All subjects either un-medicated (78%) or receiving conventional treatments at baseline
  – Subjects genotyped for COMT val108/158met SNP
## Experiment: Interactions between COMT genotype and cognitive change with clozapine

### Appendix B: Description of cognitive battery.

<table>
<thead>
<tr>
<th>Test</th>
<th>Brief Description</th>
<th>Dependent Variable</th>
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<tbody>
<tr>
<td><strong>Working Memory</strong></td>
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<tr>
<td>Auditory Consonant Trigrams</td>
<td>Subjects are given three consonants aloud and asked to repeat them after a delay of 15 seconds. During the delay subjects are required to count backward from a variable starting number.</td>
<td>Total number of correct letters recalled, irrespective of order, over 14 trials.</td>
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<tr>
<td><strong>Processing Speed</strong></td>
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<tr>
<td>WAIS-R Digit Symbol</td>
<td>Subjects are presented with sheet of paper consisting of 133 boxes that contain a number (1-9) in the top portion of each box. Subjects must draw the symbol that is paired with each number in the lower portion of each box. A key indicating the unique symbol that is paired with each number is presented at the top of the sheet.</td>
<td>Number of correctly matched symbols drawn in 2 minutes</td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
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<tr>
<td>Wisconsin Card Sorting Test</td>
<td>See reference listed in text for detailed description</td>
<td>Number of categories achieved</td>
</tr>
<tr>
<td>WISC-R Mazes (with no time limits)</td>
<td>Subjects are required to draw the correct path to the exits of a series of nine mazes of increasing complexity. Number of errors is deducted from the maximum attainable score of 30 and converted to an age-scaled score.</td>
<td>Age-scaled score (average=10)</td>
</tr>
<tr>
<td><strong>Verbal Fluency</strong></td>
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<tr>
<td>Category Instance Generation Test</td>
<td>Subjects are required to generate as many category examplars as possible in 1 min. 4 trials are given- objects found outside, animals, fruits, and vegetables.</td>
<td>Total number of words generated</td>
</tr>
<tr>
<td>Controlled Oral Word Association Test</td>
<td>Subjects are required to generate as many words as possible that start with the letters F, A, S. Three trials lasting 1 min each are given for each letter.</td>
<td>Total number of words generated</td>
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<td><strong>Verbal Learning and Memory</strong></td>
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<tr>
<td>Buschke Selective Reminding Test</td>
<td>Subjects are read aloud a list of 12 words until they can accurately recall the list without missing any word over 2 consecutive trials. Only words not recalled by subjects on two consecutive trials are repeated during the encoding stage. Subjects are then asked to repeat the list, without reminders, after attainment of list and again after a 45-min delay.</td>
<td>Number of words recalled after attainment (immediate recall)</td>
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<td></td>
<td></td>
<td>Number of words recalled after 45-min delay (delayed recall)</td>
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Experiment: Interactions between COMT genotype and cognitive change with clozapine

• **Methods**
  - Cognitive tests reduced to three domains:
    • Verbal Learning and Memory – ACTT, BSRT, WISC-Mazes
    • Attention and Verbal Fluency- DSST, COWAT, CIGT
    • Executive Function- WCST categories and % PEs
    • Global Cognitive Score calculated (mean of all tests). Global and Domains scores standardized to matched control sample
  - Linear mixed model (LM) analysis used
    • LM analysis uses maximum likelihood method for estimating means rather than method of moments (which requires complete data)
    • LM analysis more powerful with missing data points
  - Baseline scores entered as covariate into all analyses
Experiment: Interactions between COMT genotype and cognitive change with clozapine

• **Results:**
  - COMT genotype x drug interaction observed on Attention and Verbal Fluency domain
Interactions between COMT genotype and cognitive change with clozapine

• Summary:
  – Several studies suggest that COMT genotype may modulate cognitive change with APDs, particularly atypical APDs
  – More studies, especially within the context of double-blind, random assignment trials are needed
  – Specificity of the interaction
    • Specific to type of medication?
    • Specific to cognitive domains?
  – Implications for outcome?
Limitations

• Neuropsychological tools commonly used not designed for pharmacological or functional genomic studies
  – Sensitivity to genomic and drug effects
  – Specificity

• Heredity of commonly used measures is poorly understood:
  – Places gene effect in context
  – Establishes upper limit for effect

• In vivo consequences of COMT genotype remain to be adequately characterized
  – PET imaging studies of extrastriatal DA release may be helpful
Limitations

- The importance of parsing the cognitive phenotype in detecting single gene effects on normal cognitive variation and interactions with cognitive improvement.

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Future Directions

• Physiological response to atypical antipsychotics is mediated by COMT genotype
  - Improvement in WM associated with reduced PFC activation in met/met subjects

Bertolino et al., 2004
END