Genetic characterization of prefrontal-subcortical interactions in humans

Third International Imaging Genetics Conference, 1/16/2007

Andreas Meyer-Lindenberg

Unit for Systems Neuroscience in Psychiatry & Neuroimaging Core Facility
Genes, Cognition and Psychosis Program
Brain function: the critical link between genetic variation and psychiatric phenotype

Genes: multiple susceptibility alleles each of small effect

Cells: subtle molecular abnormalities

Systems: abnormal information processing

Behavior: complex functional interactions and emergent phenomena
Complex path from gene to behavior

Caudate Nucleus

- C shaped structure
- Lateral wall of lateral ventricle
- Head, body and tail of caudate are parallel to anterior horn, body and inferior horn of the lateral ventricle
Putamen and Globus Pallidus

- Putamen + Globus Pallidus = lentiform or lenticular nuclei
- Fills in space between the inferior horn and the anterior horn and body of the lateral ventricle.
- Gap between the lentiform nuclei and the lateral ventricle filled by the caudate nucleus.
- The posterior limb of the internal capsule separates the lentiform nuclei from the thalamus.
• Subthalamic nucleus
• Substantia nigra
• Ventral tegmental area
Organization of inputs to basal ganglia
Organization of basal ganglia outputs

- Caudate and putamen
- Globus pallidus external
- Globus pallidus internal
- Subthalamic nucleus

- Premotor cortex
- VA/VL complex (thalamus)

- Caudate nucleus
- VA/VL thalamic nuclear complex
- Subthalamic nucleus
- Globus pallidus, internal segment
- Globus pallidus, external segment
All regions of cerebral cortex project to the basal ganglia, but output of basal ganglia is directed towards the frontal lobe, particularly pre-motor and supplementary motor cortex.
Parallel Circuits

Neuronal circuitry of the basal ganglia
Prefrontal function and subcortical dopaminergic activity are related.

From Weinberger, 1987

Pycock et al 1980
Luillot et al 1987
Jaskiw et al 1988
Deutch et al 1989
Kolachana et al 1997
Saunders et al 1998
Roberts et al 1999
Bertolino et al 2000, 2001
The COMT val<sup>158/108</sup>met polymorphism

“high-activity”
thermo-stable
ancestral allele

“low-activity”
thermo-labile
human allele

G<sup>1947</sup> → A<sup>1947</sup>
COMT-MB/S:
Val<sup>158/108</sup> → Met<sup>158/108</sup>

SOURCE: NCBI, GEN-BANK, ACCESSION # Z26491
Dopamine terminals in striatum and in prefrontal cortex are not the same

Prefrontal dopamine and catechol-O-methyl transferase (COMT)
A unique relationship...

• scarcity of prefrontal synaptic dopamine transporters

• COMT knockout mice have increased prefrontal DA and enhanced memory (Gogos et al 1998; Kneavel et al 2000)

• COMT accounts for more than 60% of DA degradation in rat PFC (Karoum et al 1994)

• COMT inhibitors enhance working memory (Khromova et al 1995; Liljequist et al 1997)

DA flux in prefrontal cortex is uniquely affected by COMT.
Random effects analysis in imaging genetics

Single subject time courses

Genetic information enters as covariate (genotypes, haplotypes)

Group map of genetic variation

Single subject activation
Effect of *COMT* genotype on frontal lobe function

**Executive cognition**

- WCST Perseverative Errors (t-scores)
- Sibs: n = 218
- Patients: n = 181
- Controls: n = 58

- genotype effect
  - F=5.41, df=2, 449; p<0.005

**Physiological efficiency**

- v v > v m > m m, SPM 99, p<0.005

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Egan et al PNAS 2001
Replication
in 124 normal subjects

Meyer-Lindenberg et al., Molecular Psychiatry 2006
Dopamine Signaling in Prefrontal Cortex

Dopamine biases pyramidal neurons to respond to sustained/consistent and not to transient excitatory inputs (i.e. DA focuses and stabilizes the response network)

Adapted from Seamans et al. J Neurosci 2001
"Inverted U Dose-response" Curve

Supported by findings from several studies:
- Arnsten and Goldman-Rakic, 1986, 1990
- Arnsten et al., 1994
- Murphy et al., 1994, 1996a, b, 1997
- Williams and Goldman-Rakic, 1995
- Verma and Moghaddam, 1996

From Goldman-Rakic 2000

Meyer-Lindenberg et al., Mol Psych 2006

N=126

Supported by findings from several studies:
- Arnsten and Goldman-Rakic, 1986, 1990
- Arnsten et al., 1994
- Murphy et al., 1994, 1996a, b, 1997
- Williams and Goldman-Rakic, 1995
- Verma and Moghaddam, 1996
COMT val158met genotype, working memory load, and response to amphetamine interact in PFC

Impact of P2 promoter SNP

Chen et al. AJHG 2004
Characterization of a risk haplotype through neuroimaging

Meyer-Lindenberg et al., *Mol Psych* 2006
‘Schifman’ haplotype (rs737865-rs4680-rs165599)
COMT genotype affects regulation of midbrain dopamine

Meyer-Lindenberg et al. Nature Neuroscience 2005a
Midbrain dopamine synthesis is linked to prefrontal cortex

Meyer-Lindenberg et al. Nature Neuroscience 2005a
Regulation of midbrain dopamine by prefrontal cortex depends on COMT genotype

Meyer-Lindenberg et al. Nature Neuroscience 2005a
Adjusted data fit the inverted-u curve
Dopaminergic tuning mechanism?

<table>
<thead>
<tr>
<th></th>
<th>met homozygotes</th>
<th>val-carriers</th>
<th>Difference of correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLPFC ROI 0-Back</td>
<td>-0.85 (p&lt;0.001)</td>
<td>0.96 (p&lt;0.001)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>DLPFC ROI 2-Back</td>
<td>-0.82 (p&lt;0.001)</td>
<td>0.96 (p&lt;0.001)</td>
<td>p&lt;.0001</td>
</tr>
<tr>
<td>DPLFC ROI Activation</td>
<td>0.59 (p&lt;0.05)</td>
<td>-0.51 (p&lt;0.05)</td>
<td>p&lt;0.02</td>
</tr>
</tbody>
</table>

Meyer-Lindenberg et al. Nature Neuroscience 2005a
<table>
<thead>
<tr>
<th>Effect on</th>
<th>Met</th>
<th>Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMT (enzyme activity)</td>
<td>Low activity</td>
<td>High activity</td>
</tr>
<tr>
<td>Synaptic DA transmission; tonic-phasic DA model</td>
<td>↑Tonic DA (extraneuronal) and ↓phasic DA (synaptic) subcortically, increased DA in cortex</td>
<td>↓Tonic DA (extraneuronal) and ↑phasic DA (synaptic) subcortically, decreased DA in cortex</td>
</tr>
<tr>
<td>Computational models of PFC and working memory function</td>
<td>↑D1 transmission; persistent Na(+)- and NMDA; ↑working memory maintenance functions</td>
<td>↑D2 transmission; AMPA; ↑working memory ‘resetting’ and ‘updating’</td>
</tr>
<tr>
<td>Dual cytoarchitectonic trends theory</td>
<td>↑Archicortical (activation), redundancy bias; mediated by medial and dorsal frontal cortex/dorsal striatum</td>
<td>↑Paleocortical (arousal), novelty bias; mediated by orbital and ventrolateral frontal cortex/amygdala–ventral striatum</td>
</tr>
<tr>
<td>Primary cognitive effect</td>
<td>Benefits on tasks demanding stability (maintenance phases of working memory, sustained execution of prepotent response sets), but may show excessive cognitive rigidity (difficulty updating or switching)</td>
<td>Benefits on tasks demanding flexibility (updating contents of working memory, switching to novel task), but may lack cognitive stability (increased distractibility, loss of cognitive sets)</td>
</tr>
<tr>
<td>Schizophrenia: symptoms and sampling issues</td>
<td>More severe negative symptoms; more common in chronic inpatient samples</td>
<td>More likely to show positive and reactive symptoms; more common in community samples</td>
</tr>
<tr>
<td>Role in the treatment of schizophrenia</td>
<td>Poor response to conventional D2-blocking agents, may respond better to D1 agonists, partial agonists, or agents that enhance D1 transmission (some NMDA antagonists; 5-HT(2A) antagonists; 5-HT(1A) agonists</td>
<td>Better response to conventional D2-blocking agents, may benefit from COMT inhibitors</td>
</tr>
<tr>
<td>Role in alcoholism and alcohol abuse</td>
<td>Associated with increased Type I alcoholism and greater alcohol use</td>
<td>Associated with decreased risk for Type alcoholism and less alcohol use</td>
</tr>
<tr>
<td>Role in violent/aggressive behavior</td>
<td>Associated with higher propensity for impulsive-aggressive behavior, especially in males</td>
<td>Associated with lower propensity for impulsive-aggressive behavior, especially in males</td>
</tr>
<tr>
<td>Role in obsessive–compulsive disorder</td>
<td>Increased risk, particularly for comorbid OCD-tic disorders</td>
<td>Decreased risk, particularly for comorbid OCD-tic disorders</td>
</tr>
</tbody>
</table>
COMT impacts on amygdala – orbitofrontal coupling

Right amygdala reference region

Drabant et al., Archives of General Psychiatry 2006
**DARPP-32**

- DARPP-32 = Dopamine- and cAMP-regulated phosphoprotein of molecular weight 32 kDa
- Potent inhibitor of PP1 and amplifier of PKA- and PKG-mediated signaling when it is phosphorylated at Thr\textsuperscript{34}. Phosphorylation at Thr\textsuperscript{75} by Cdk5 converts DARPP-32 into an inhibitor of PKA.
- Central molecular switch integrating multiple information streams (neurotransmitters, neuromodulators, neuropeptides, steroid hormones) converging onto dopaminceptive neurons
- DARPP-32 dependent regulation central to response to antidepressants, neuroleptics, and drugs of abuse, and impacts on neural plasticity.

Svenningson et al. Ann Rev Pharmacol 2004
DARPP-32: integrator of neurotransmission at dopaminoceptive neurons

Ouimet et al.
J Comp Neurol 1992

Svenningson et al. Ann Rev Pharmacol 2004
Genetic variation in PPP1R1B, identified through resequencing

Meyer-Lindenberg et al. J Clinical Investigation, in press
Haplotype frequencies in CBDB/NIMH sample, 7-SNP haplotype

<table>
<thead>
<tr>
<th>M03</th>
<th>M04</th>
<th>M11</th>
<th>M12</th>
<th>M13</th>
<th>M14</th>
<th>M15</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>G</td>
<td>A</td>
<td>T</td>
<td>G</td>
<td>T</td>
<td>C</td>
<td>A</td>
<td>14.1%</td>
</tr>
<tr>
<td>C</td>
<td>G</td>
<td>T</td>
<td>G</td>
<td>T</td>
<td>C</td>
<td>C</td>
<td>3.5%</td>
</tr>
<tr>
<td>C</td>
<td>G</td>
<td>T</td>
<td>G</td>
<td>T</td>
<td>C</td>
<td>A</td>
<td>2.1%</td>
</tr>
<tr>
<td>C</td>
<td>A</td>
<td>C</td>
<td>A</td>
<td>C</td>
<td>T</td>
<td>C</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Meyer-Lindenberg et al. J. Clinical Investigation, in press
DARPP-32 mRNA expression

Meyer-Lindenberg et al. J Clinical Investigation, in press
FBAT: association with cognitive phenotypes

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Haplotype global</th>
<th>MTHF haplotype association</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0CAGCTC</td>
<td></td>
<td>Schizophrenia association</td>
</tr>
<tr>
<td>0.001</td>
<td>0.054</td>
<td>D diet</td>
</tr>
<tr>
<td>0.023</td>
<td>0.011</td>
<td>CVLT15 Std Score</td>
</tr>
<tr>
<td>na</td>
<td>na</td>
<td>Letter Fluency</td>
</tr>
<tr>
<td>0.013</td>
<td>0.010</td>
<td>Nback-one</td>
</tr>
<tr>
<td>0.047</td>
<td>na</td>
<td>Nback-two</td>
</tr>
<tr>
<td>(0.060)</td>
<td>na</td>
<td>Nback-three</td>
</tr>
<tr>
<td>0.023</td>
<td>na</td>
<td>TrailsA</td>
</tr>
<tr>
<td>0.008</td>
<td>0.008</td>
<td>TrailsB</td>
</tr>
<tr>
<td>0.002</td>
<td>0.001</td>
<td>WAIS Est Full Scale IQ</td>
</tr>
<tr>
<td>0.028</td>
<td>0.013</td>
<td>WCST Category Score</td>
</tr>
<tr>
<td>(0.084)</td>
<td>0.014</td>
<td>WCST Pont PET Score</td>
</tr>
<tr>
<td>na</td>
<td>na</td>
<td>WMSR Log Mem 1</td>
</tr>
<tr>
<td>na</td>
<td>na</td>
<td>WMSR Log Mem 2</td>
</tr>
<tr>
<td>(0.071)</td>
<td>0.029</td>
<td>WMSR VPA1 Total</td>
</tr>
<tr>
<td>0.016</td>
<td>0.003</td>
<td>WRAT</td>
</tr>
</tbody>
</table>

Meyer-Lindenberg et al. J Clinical Investigation, in press
Genetic variation in PPP1R1B predicts striatal structure and function and frontostriatal interactions

Structure
Meyer-Lindenberg et al. J Clinical Investigation, in press

N-back working memory

Emotional faces
Basic Circuit of Basal Ganglia

Cerebral Cortex

Neostriatum

GPi/SNpr

VA/VL thalamus
Conclusions

- A very frequent PPP1R1B haplotype is associated with risk for schizophrenia, efficient striatal activation and increased frontostriatal connectivity.
- Similar data have been found in drug-naïve schizophrenia, where deficient striatal gating has been proposed.
- However, efficient striatal activation and extensive connectivity is important for striatal filtering and the haplotype was associated with improved cognitive function.
- Since frontostriatal connectivity is critical for cognitive function in normals, possible neural mechanism for balancing selection maintaining frequent haplotype.
Proline Dehydrogenase

Rate limiting enzyme in Glutamate synthesis and functions in redox reactions in mitochondria
From Graybiel, A. Neural Networks, Am J Psychiatry 2001
rs372055
Leu synon

rs450046
120% enzymatic activity

rs2870983
<30% enzymatic activity

rs4819756
<30-70% enzymatic activity

PRODH

Bender, 2005
PRODH Schizophrenia Association Study


PRODH and Startle


<table>
<thead>
<tr>
<th>rs450046 Q521R</th>
<th>FBAT TDT Single snps</th>
<th>FBAT TDT Positive haplotype Global p=0.022</th>
<th>FBAT TDT Negative haplotype Global p=0.022</th>
<th>Case-control positive haplotypes Global p=0.034</th>
<th>Case-control negative haplotypes Global p=0.034</th>
<th>Attention: control Haplotypes Global p=0.028</th>
</tr>
</thead>
<tbody>
<tr>
<td>120% activity</td>
<td>+2.409 (2) p=0.026</td>
<td>2 P=0.007</td>
<td>1 P=0.022</td>
<td>2     p=0.07</td>
<td>1     p=0.032</td>
<td>1 P=0.015</td>
</tr>
<tr>
<td>50 families</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>-2.305 (1) p=0.033</td>
<td>1 P=0.007</td>
<td>1 P=0.022</td>
<td>1     p=0.07</td>
<td>1     p=0.032</td>
<td>1 P=0.015</td>
</tr>
<tr>
<td>37 families</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>rs2870983 A472T</td>
<td>-2.153 (1) p=0.043</td>
<td>1 P=0.007</td>
<td>2 P=0.022</td>
<td>2     p=0.07</td>
<td>2     p=0.032</td>
<td>1 P=0.015</td>
</tr>
<tr>
<td>&lt;30% activity</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>110 families</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>rs4819756 R185W</td>
<td>-2.153 (1) p=0.043</td>
<td>1 P=0.007</td>
<td>2 P=0.022</td>
<td>2     p=0.07</td>
<td>2     p=0.032</td>
<td>1 P=0.015</td>
</tr>
<tr>
<td>30-70%</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>110 families</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>0.011</td>
</tr>
</tbody>
</table>

**rs450046 Q521R** 120% activity

**rs2870983 A472T** <30% activity

**rs4819756 R185W** 30-70%
Imaging in Normal controls

- 13 SNPs picked using Hapmap release 20 aggressive Tagger in Haploview were phased in 373 Caucasian with Phase 2.1 (Stephens, 2001) for 74 probable haplotypes.
- Haplotypes were then recoded to 3 SNP haplotype of functional snps.
Optimized VBM for PRODH Haplotypes

138 healthy right handed volunteers of European ancestry with no current or prior history of psychiatric or neurological illness.

- Protective haplotype > reference haplotype cluster maximum -20, 60, 1
  \[ Z=4.38, \text{whole brain FDR 0.050 p < 0.001} \]

- Risk haplotype < reference haplotype cluster maximum 22, 19, -6
  \[ Z=3.92, \text{FDR=0.070, p < 0.001 with striatal ROI.} \]
A systems approach to complex genetics in psychiatry

Genes:
- multiple susceptibility alleles each of small effect

Cells:
- subtle molecular abnormalities

Systems:
- abnormal information processing

Behavior:
- complex functional interactions and emergent phenomena
Thanks
Unit for Systems Neuroscience in Psychiatry

Other Collaborators:
- Tom Nichols, U Michigan
- Peter Kirsch, Giessen
- Ed Bullmore, Cambridge
- John Swaddle, William & Mary
- Carolyn B. Mervis, U Louisville
- Colleen A. Morris, U Nevada
- James Fallon, UCI

Neuroimaging Core Facility:
- Anand Mattay
- Lukas Pezawas
- Joshua Buckholtz
- Beth Verchinski
- Ahmad Hariri
- Emily Drabant
- Karen Munoz
- Aaron Goldman
- Robyn Honea
- Ashley Wabnitz
- Lisa Wiedholz
- Giuseppe Blasi
- Qiang Chen

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- Ashley Wabnitz
- Lisa Wiedholz
- Giuseppe Blasi
- Qiang Chen
The puzzle of complex psychiatric genetics

- Polygenic, heterogeneous disorders
- Generally weak risk effects
- Epistasis and gene-environment interactions
- Most identified polymorphisms are not “functional” (in the conventional sense)

Goldman et al Nat Rev Gen 2005
Connections

- **Afferents/inputs (neostriatum):**
  - Cerebral cortex (entire cortex)
  - Thalamus (intralaminar and midline nuclei)
  - Amygdala (basolateral nucleus)
  - Raphe, substantia nigra pars compacta, VTA

- **Efferents/output (GPi, VP, SNpr):**
  - Ventral tier nuclei of thalamus
  - Subthalamic nucleus
  - Superior colliculus
The basal ganglia include...

- Neostriatum
  - Caudate nucleus
  - Putamen
  - Nucleus Accumbens
- Globus Pallidus
  - Internal segment
  - External segment
  - Ventral pallidum
- Subthalamlic nucleus
- Substantia nigra
  - Pars compacta
  - Pars reticulata
- Pedunculopontine nucleus**