Genetic influences on human frontal cortical networks

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Disclosures

Speakers bureau: none
Consultant: none
Advisory boards: none
Equity interest: none
Salary support: St Jude Medical, 2011-13 (5%)
Off-label uses: none
Grant support: National Institutes of Health
University of Michigan Department of Psychiatry
University of Michigan Depression Center
Taubman Medical Research Institute
Acknowledgements

University of Michigan
Jon-Kar Zubieta
David Hsu
Marta Pecina
Tiffany Love
Mary Heitzeg
Tal Shafir
Heng Wang
Susan Kennedy

University of Pennsylvania
Falk Lohoff

NIAAA
David Goldman
Laura Bevilacqua
Zhifeng Zhou
Elizabeth Heinz
Pei-Hong Shen
Colin Hodgkinson

University of Illinois Chicago
Scott Langenecker
Sara Weisenbach
Overview

Genes, environment, risk, and the brain

Four genes that influence frontal-cingulate emotion circuitry
- **NPY** neuropeptide Y
- **VMAT1** vesicular monoamine transporter 1
- **CRHR1** corticotrophin releasing hormone receptor 1
- **DRD2** dopamine D2 receptor

Summary and future directions
Genes, environment, and risk

- Genetic variation
- Vulnerable brain (or resilient)
- Disordered brain
  - Depression
  - Anxiety
  - Addiction
  - Psychosis

Early experience

Stress

Photo credit: Becky Wetherington
Today's focus

Which variable genetic factors give rise to variation in emotional brain function?

Variant $X$ is functional in vitro and has been implicated in psychiatric disorders.

Is $X$ associated with altered function of neural region $Y$?

Altered $Y = \text{candidate intermediate phenotype}$
Imaging prefrontal emotion processing in humans

Functional magnetic resonance imaging (fMRI)
Blood oxygen level dependent (BOLD) response
Indirect measure of neural activity

Emotion word task
93 healthy adults and 18 with major depression

war  lost  burial  negative
iron  journal  fur  neutral
Neuropeptide Y
A regulator of the brain’s stress response

NPY is a 36-amino-acid peptide neurotransmitter evolutionarily conserved widely distributed in the brain expressed at high concentrations

Neuropeptide Y is co-released with other neurotransmitters, including GABAergic interneurons in the cortex and striatum
(Kask et al., Neurosci Biobehav Rev, 2002)

Experiments in animal models indicate that stress increases expression and release of NPY in the amygdala and that NPY reduces anxiety-like behavior
(Heilig, Neuropeptides, 2004; Rhinehart et al., 2009)
Neuropeptide Y
Implicated in neuropsychiatric disease

Peripheral NPY has been positively associated with resilience to psychological stress

Low NPY concentrations in plasma, cerebrospinal fluid, and postmortem brain have been variably associated with mood disorders

A single-nucleotide polymorphism in the NPY gene was linked with treatment-resistant major depressive disorder
(Heilig et al., J Psychiatr Res, 2004)

Variation in NPY expression is influenced by variation in the NPY gene
Does *NPY* variation affect prefrontal emotion processing in humans?

*NPY Low* → ? → response to negative emotion → mood and anxiety disorders
Functional genetic variation of NPY

Six-marker haplotype
(Zhou et al., Nature, 2008)

Individuals with low-expression NPY genotypes exhibited:

- lower endogenous opioid release during pain
- greater amygdala responses to threat-related stimuli
- greater trait anxiety

Effects of NPY variation on prefrontal function in humans

Increased response to negative words in the Low NPY group

medial prefrontal cortex
anterior cingulate cortex

Gene effects persisted when adjusting for age, sex, and ancestry

Mickey et al., Arch Gen Psychiatry, 2011
NPY effects on emotion phenotypes

Affective state during pain-stress challenge \((n = 78)\)

Association with depression

Mickey et al., *Arch Gen Psychiatry*, 2011
Summary:  *NPY* variation and neural processing of emotion

Low-expression variants of the *NPY* gene increase responsiveness of medial PFC and pregenual ACC to negative words.

Preliminary data suggest effects of *NPY* on response of nucleus accumbens monetary loss.

*NPY*-driven variation in prefrontal, cingulate, and accumbens response to negative stimuli is a potential endophenotype for mood and anxiety disorders.

Low *NPY* expression by cortical and striatal interneurons may heighten the sensitivity to negative stimuli, thereby increasing risk of psychiatric illness.
Vesicular monoamine transporter 1
A key enzyme in neuronal monoamine storage

Packages monoamine transmitters into synaptic vesicles
  serotonin (5HT)
  dopamine (DA)
  norepinephrine (NE)

Two vesicular monoamine transporters
  VMAT1
  VMAT2

VMAT1 relatively selective for serotonin
Vesicular monoamine transporter 1
Implicated in neuropsychiatric disease

Pharmacologic blockade of VMAT causes depression in humans

Several coding variants in VMAT1 gene (SLC18A1)

Thr136 associated with bipolar disorder (Lohoff et al., Neuropsychopharm, 2006)

Thr136 has lower activity in vitro

No effects of Thr4Pro or Ser98Thr

Lohoff et al., Mol Psychiatry, 2013
Does *VMAT1* variation influence emotion processing in humans?

VMAT Thr136 → ? → brain image → response to negative emotion → mood disorders
Effects of *VMAT1* variation on prefrontal function

Greater activation among Thr136 homozygotes
- medial prefrontal cortex
- anterior cingulate cortex

Gene effects persisted when adjusting for age, sex, ancestry, and diagnosis

No significant effects of putatively non-functional variants Thr4Pro and Ser98Thr

Lohoff et al., *Mol Psychiatry*, 2013
Summary: *VMAT1* variation and emotion processing

*VMAT1*-driven variation in prefrontal activation with negative emotion is a potential endophenotype for psychiatric disorders

Thr136 may cause less efficient filling of monoamine vesicles, reducing frontal release of monoamines, increasing metabolic activity

Lower functioning allele Thr136 associated bipolar disorder, but rare hyper- and hypo-functional alleles may also be associated (Lohoff et al., *Mol Psychiatry*, 2013)

*VMAT1* genotype could contribute to variation in brain or clinical responses to monoaminergic drugs
Corticotrophin releasing hormone receptor 1
Autonomic, hormonal, and behavioral response to stress

CRHR1 rs110402
single nucleotide variant

G allele associated with major depressive disorder (MDD) in context of childhood abuse
(Bradley et al., 2008; Polanczyk et al., 2009; Heim et al., 2009; Tyrka et al., 2009; Ressler et al., 2010)

Hyper-activation of subgenual anterior cingulate cortex in MDD patients among GG homozygotes but not A carriers

Hsu, Mickey, et al., J Neurosci, 2012
D2 dopamine receptor
Processing of emotionally salient stimuli

DRD2 rs4274224
single nucleotide variant
- intronic, function unknown

Greater activation of pregenual and subgenual anterior cingulate cortex in GG and AA homozygotes

Similar genetic effects in hemodynamic responses to monetary reward and dopamine release with pain

Pecina, Mickey, et al., Cortex, 2012
Overall summary

Common, putatively functional, genetic variants (*NPY, VMAT1, CRHR1, DRD2*) influence medial prefrontal and anterior cingulate responses to negative stimuli.

Variation in stress- and emotion-sensitive circuitry across individuals may mediate risk for psychiatric disorders, and/or moderate response to specific treatments.

These genetic causes of variation in brain function could be examined in experimental animals.

Interactions of these genes with specific environmental factors (childhood adversity, recent stress) should be examined in humans and animal models.
Speculative model framework

- Childhood emotional abuse
- NPY
- CRHR1
- VMAT1
- DRD2
- Vulnerable brain
- Disordered brain
- Depression
- Anxiety
- Addiction
- Psychosis
- Concussion
- Stress

Photo credit: Becky Wetherington
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