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

Ackowledgements

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

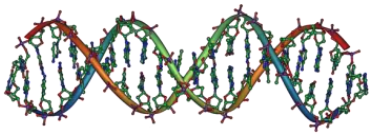
Genes, environment, risk, and the brain

Four genes that influence frontal-cingulate emotion circuitry

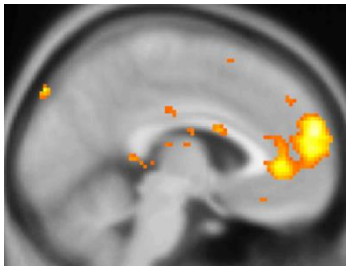
NPY	neuropeptide Y
VMAT1	vesicular monoamine transporter 1
CRHR1	corticotrophin releasing hormone receptor 1
DRD2	dopamine D2 receptor

Summary and future directions

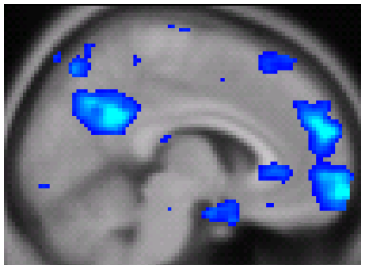
Genes, environment, and risk



genetic variation

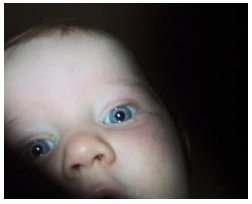


vulnerable brain
(or resilient)



disordered brain

depression
anxiety
addiction
psychosis



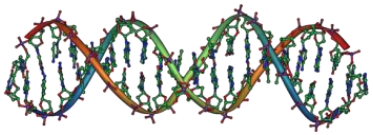
early experience

stress

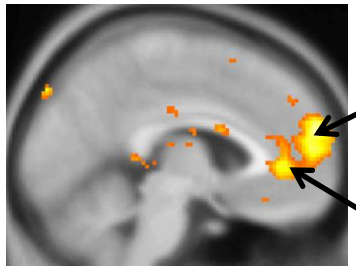
Photo credit: Becky Wetherington

Today's focus

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



genetic variation



vulnerable brain

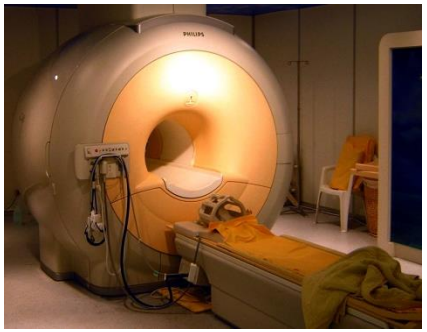
Variant ***X*** is functional *in vitro* and has been implicated in psychiatric disorders

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

Altered ***Y*** = candidate intermediate phenotype

Imaging prefrontal emotion processing in humans

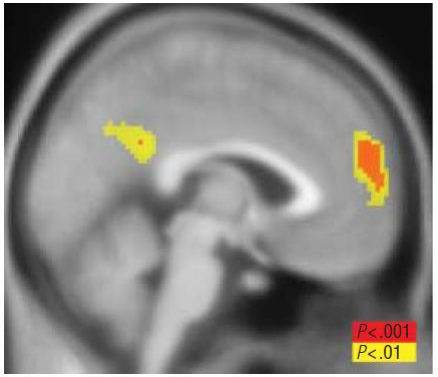
Functional magnetic resonance imaging (fMRI)
Blood oxygen level dependent (BOLD) response
Indirect measure of neural activity



Emotion word task
93 healthy adults and 18 with major depression

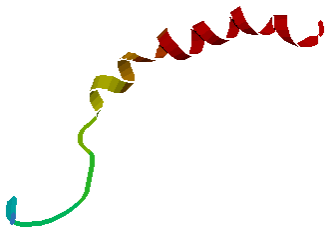
war lost burial — negative

... iron journal fur — neutral



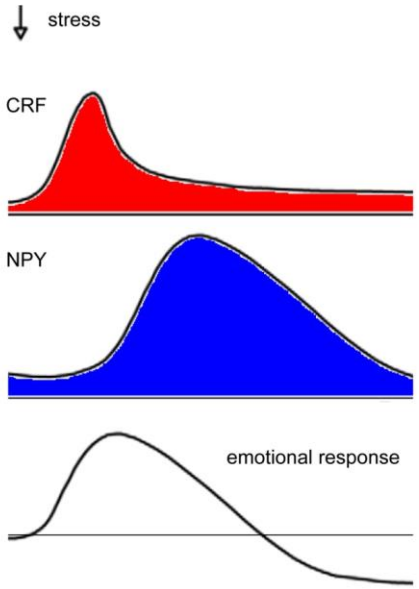
Neuropeptide Y
A regulator of the brain's stress response

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

(Morgan et al., *Biol Psychiatry*, 2000, 2002, 2003; Yehuda et al., Biol Psychiatry, 2006)

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

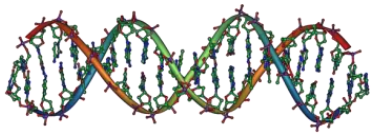
A single-nucleotide polymorphism in the *NPY* gene was linked with treatment-resistant major depressive disorder

(Heilig et al., *J Psychiatr Res*, 2004)

Variation in NPY expression is influenced by variation in the *NPY* gene

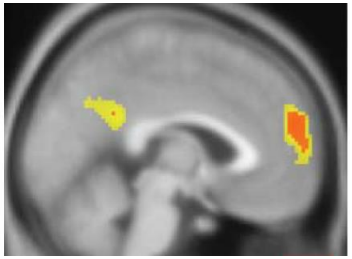
(Heilig et al., *J Psychiatr Res*, 2004; Zhou et al., *Nature*, 2008)

Does *NPY* variation affect prefrontal emotion processing in humans?



NPY Low

?



response to
negative emotion

...

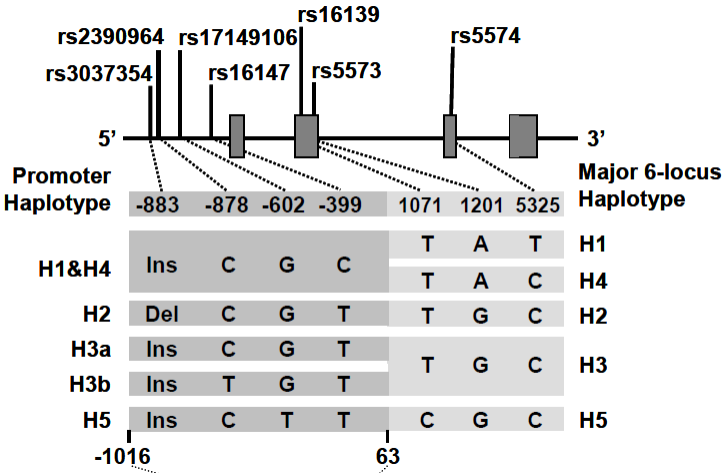
mood and
anxiety
disorders

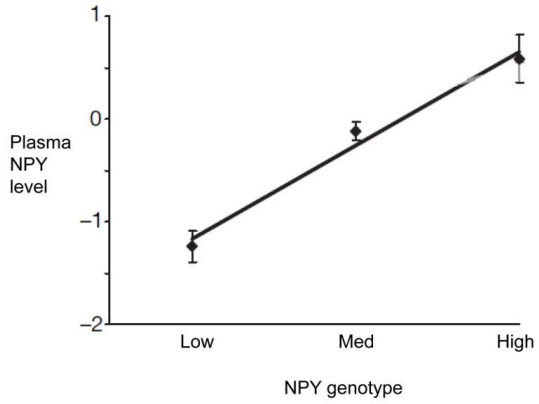
Functional genetic variation of NPY

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





modified from Zhou et al., *Nature*, 2008

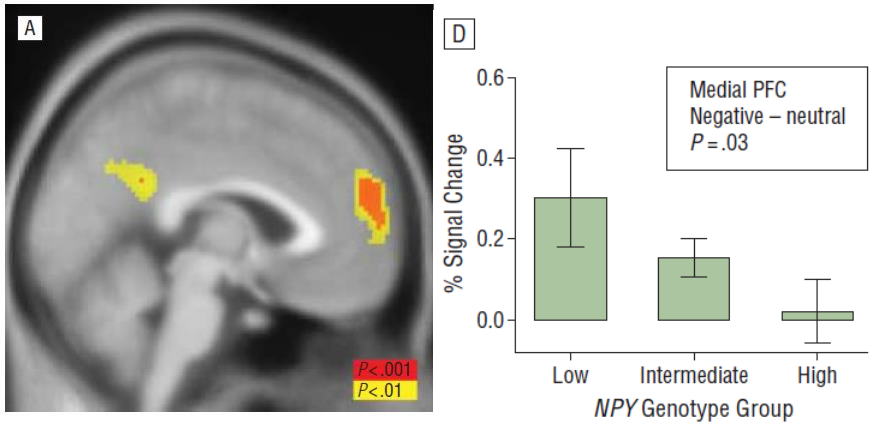
Effects of *NPY* variation on prefrontal function in humans

Increased response to negative words in the Low NPY group

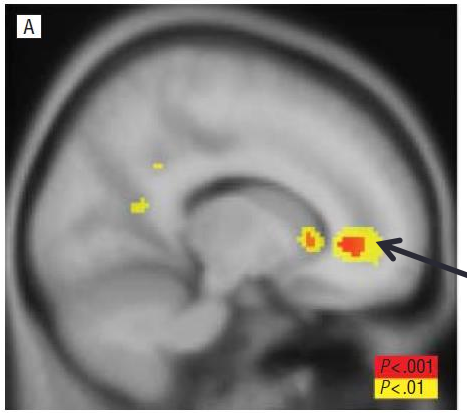
- medial prefrontal cortex
- anterior cingulate cortex

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

Region-of-interest



Whole-brain

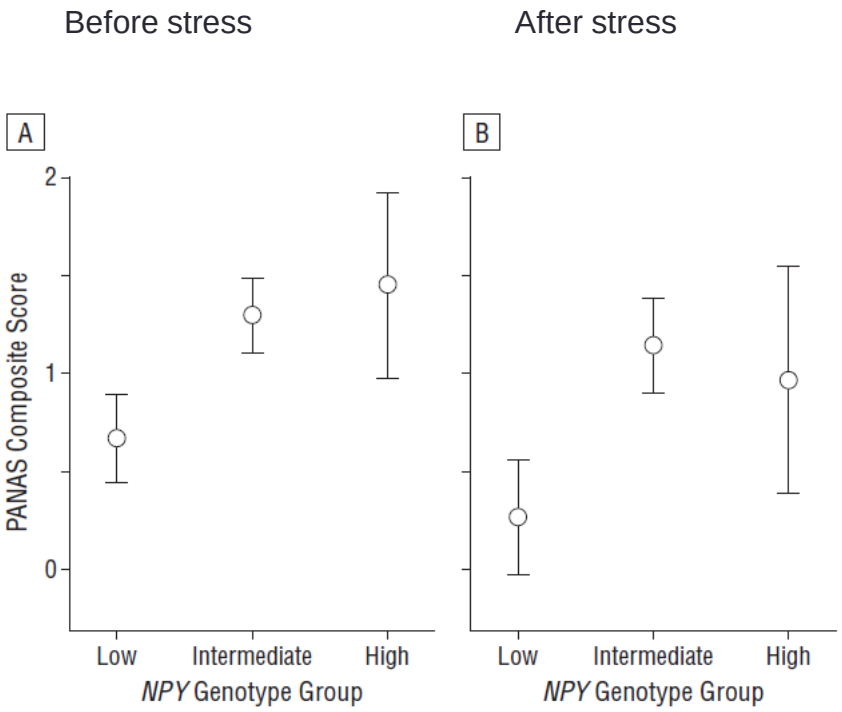


pregenual ACC
P < 0.05, corrected

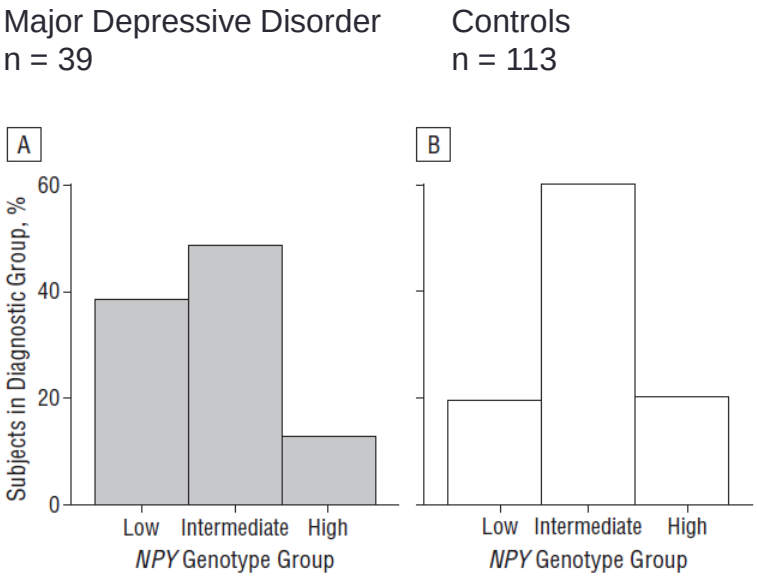
Mickey et al., *Arch Gen Psychiatry*, 2011

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

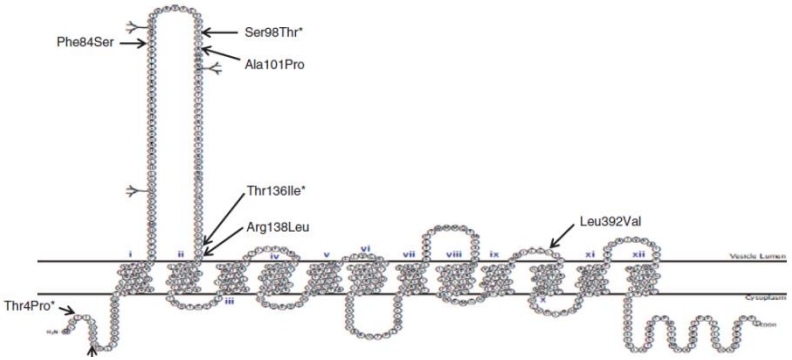
NPY-driven variation in prefrontal, cingulate, and accumbens response to negative stimuli is a potential endophenotype for mood and anxiety disorders

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

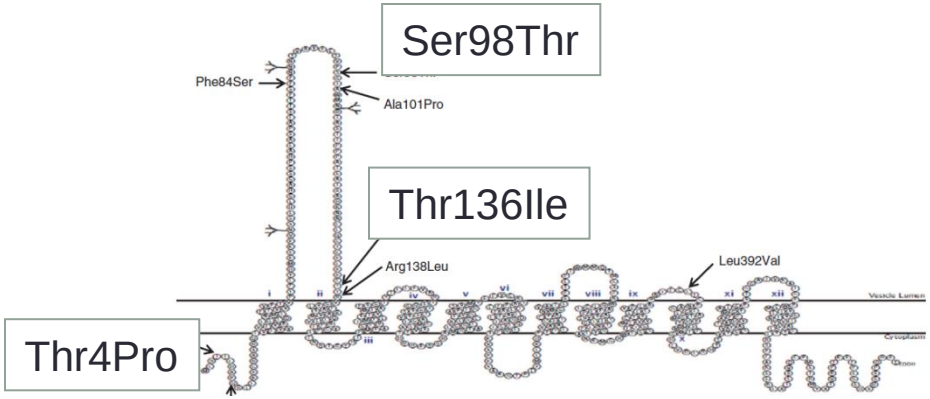
Pharmacologic blockade of VMAT causes depression in humans

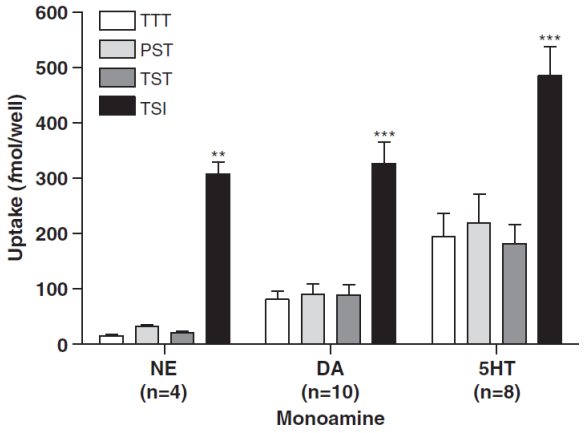
Several coding variants in *VMAT1* gene (*SLC18A1*)

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

Thr136 has lower activity *in vitro*

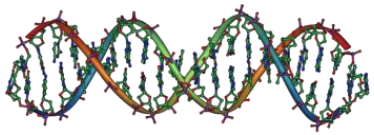
No effects of Thr4Pro or Ser98Thr





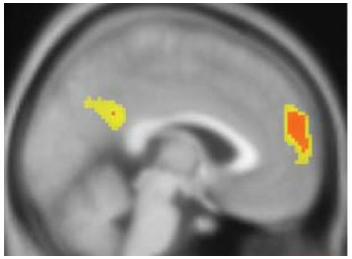
Lohoff et al., *Mol Psychiatry*, 2013

Does *VMAT1* variation influence emotion processing in humans?



VMAT Thr136

?



response to
negative emotion

...

mood
disorders

Effects of *VMAT1* variation on prefrontal function

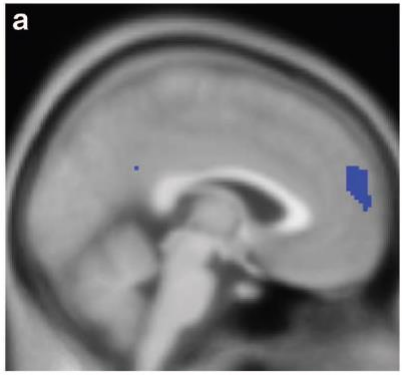
Greater activation among Thr136 homozygotes

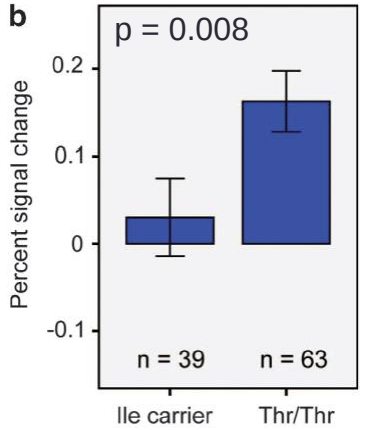
medial prefrontal cortex
anterior cingulate cortex

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

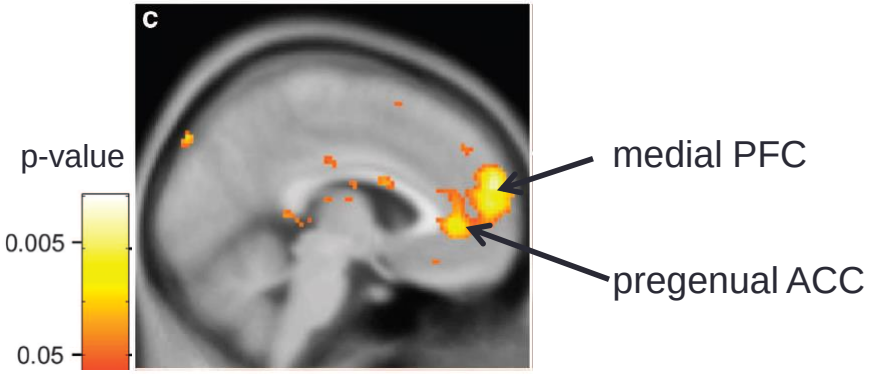
No significant effects of putatively non-functional variants Thr4Pro and Ser98Thr

Region-of-interest





Whole-brain



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)

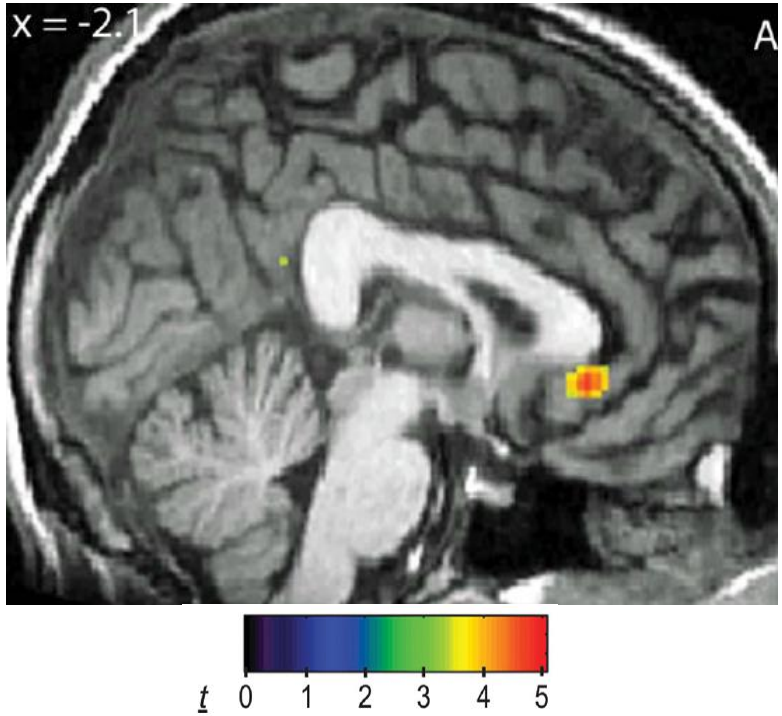
VMAT1 genotype could contribute to variation in brain or clinical responses to monoaminergic drugs

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



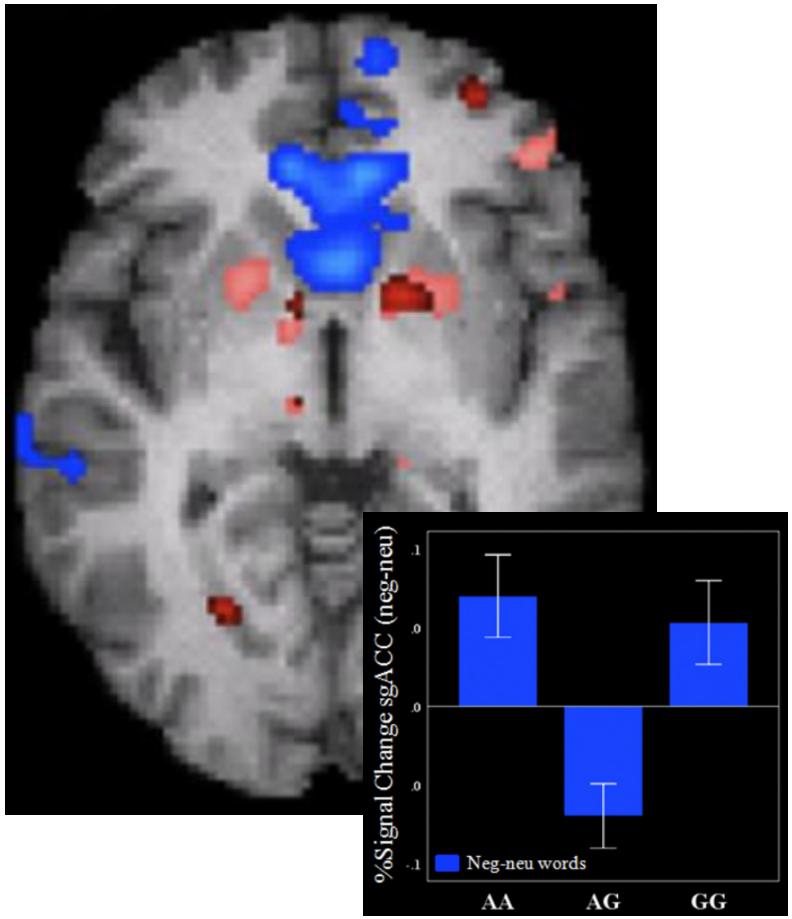
Hsu, Mickey, et al., *J Neurosci*, 2012

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

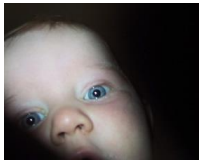
Common, putatively functional, genetic variants (*NPY, VMAT1, CRHR1, DRD2*) influence medial prefrontal and anterior cingulate responses to negative stimuli

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

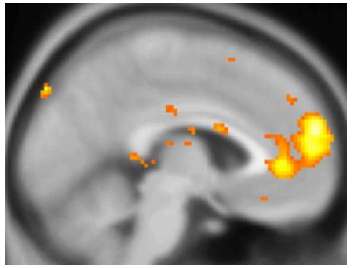
Speculative model framework



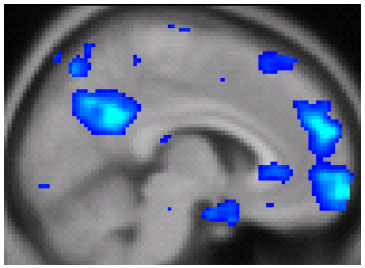
childhood emotional abuse

NPY

CRHR1



vulnerable brain



disordered brain

depression
anxiety
addiction
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VMAT1

DRD2

concussion

stress

Photo credit: Becky Wetherington

Ackowledgements

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