Quantitative approaches in behavioral neuroscience

1st ISBS Summer School

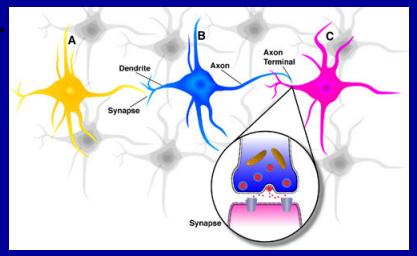
St. Petersburg, Russia

May 9th -15th,2008

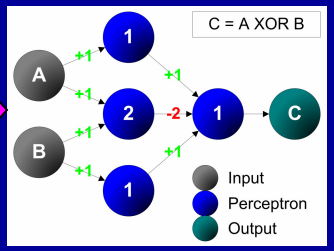
From neurons to complex behaviors

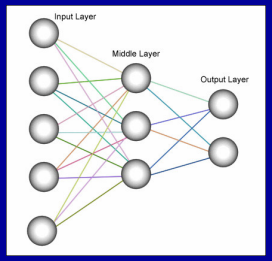
Neurons

Biological neural networks



"Model" neural networks

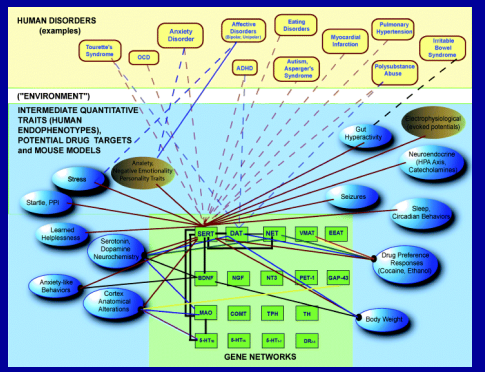




Key brain processes:
Imaging Decision Action

Complex animal behaviors

Translating animal behavior into complex human phenotypes

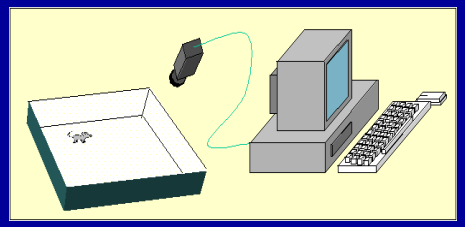


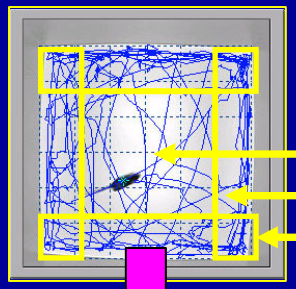
Models of human brain disorders

Quantification of animal behaviors

I. Analysis of quantity vs. quality/patterning

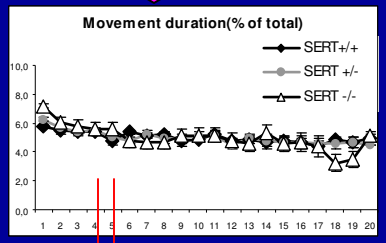
- spatial
- temporal
- spatio-temporal

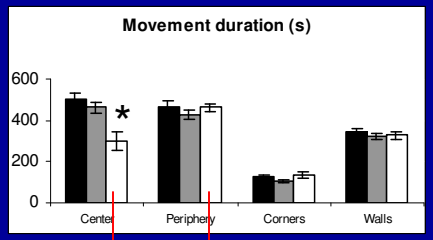




Center
Periphery
Corners

Kalueff et al., 2007, in press





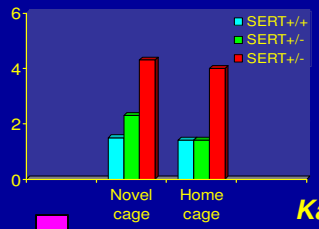
Activity
Exploration
Anxiety
Cognitions

Domains

II. Confronting behavioral domains

Example: marble burying test

- Anxiety
- Activity



Kalueff et al., 2006

Hypo-locomotion

Anxiety

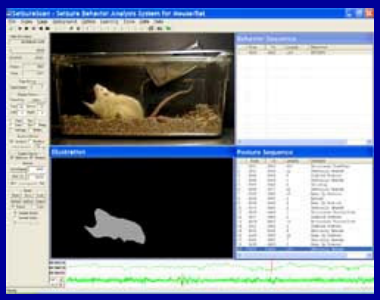
Building phenotype networks

Defining endo-phenotypes:

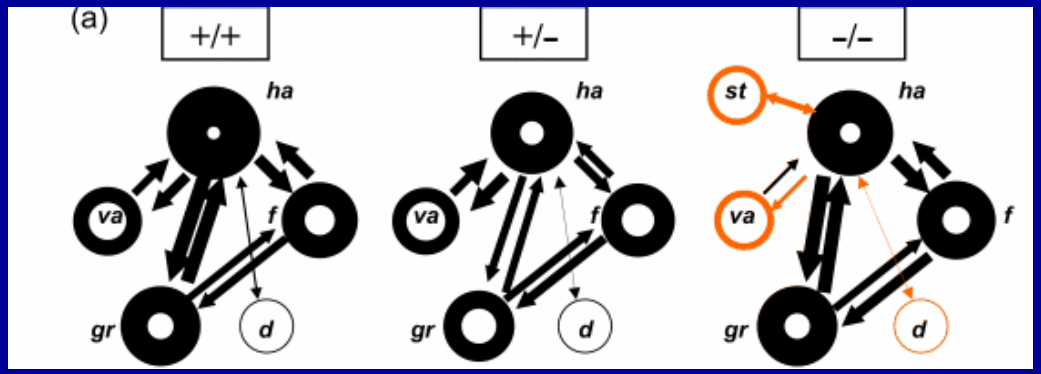
↓ Locomotion
↑ Anxiety or emotionality
Unaltered spatial memory
Use of different spatial strategies

Other data-mining approaches

- Correlation analysis
- Principal component analysis
- Analysis of ***microbehaviors*** →
- Assessment of behavioral ***organization***

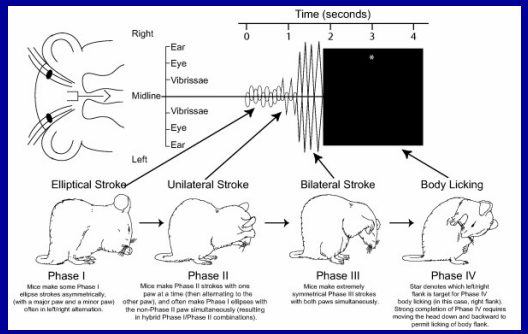


E.g.: ethograms



Kalueff et al., 2007, Genes Brain Behav

Clever System Inc

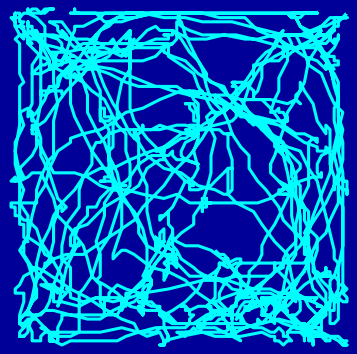


E.g., grooming

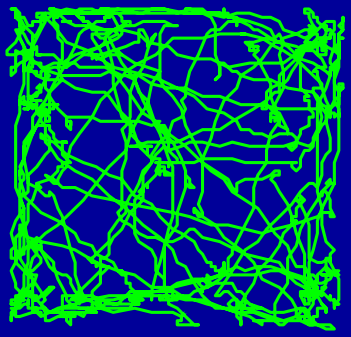
Berridge et al., 2005

→ **Better models of behaviors**

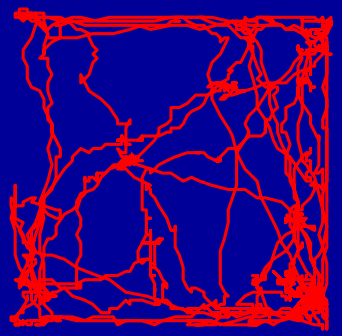
Towards better models of behaviors



+/+

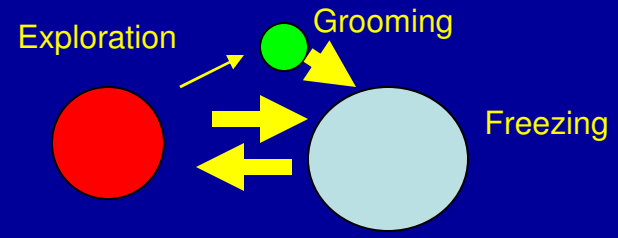


+/-

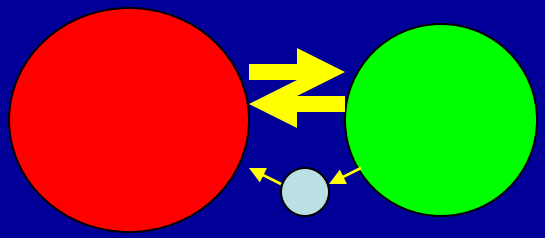


-/-

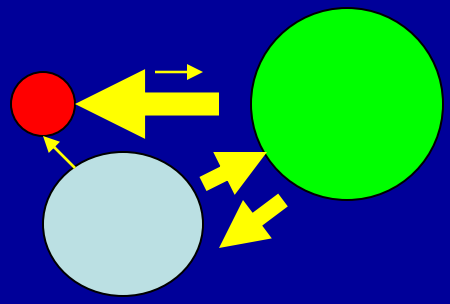
Thigmotaxis:
High anxiety



High anxiety



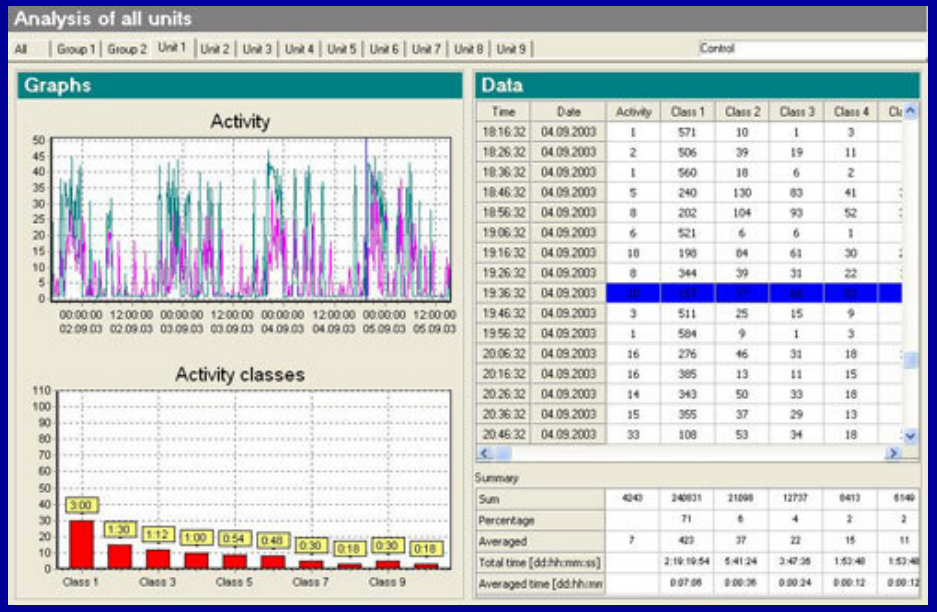
OCD-like behavior

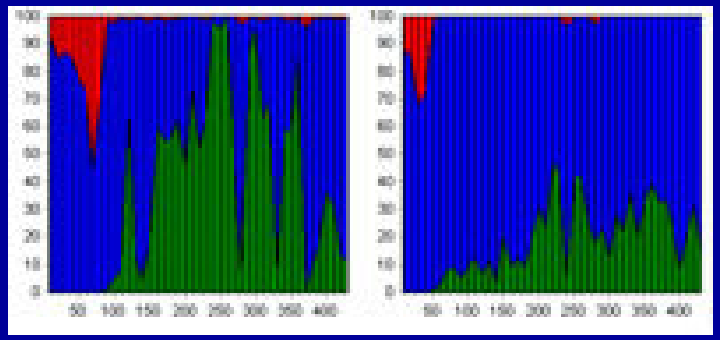


Depressive phenotype

Can be used to create artificial models of aberrant behaviors

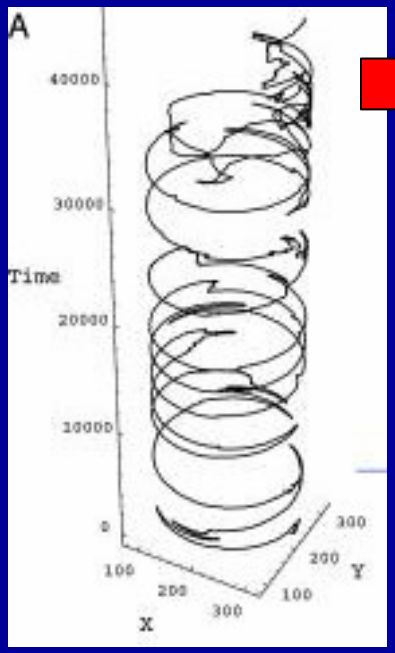
Extensive automated phenotyping systems

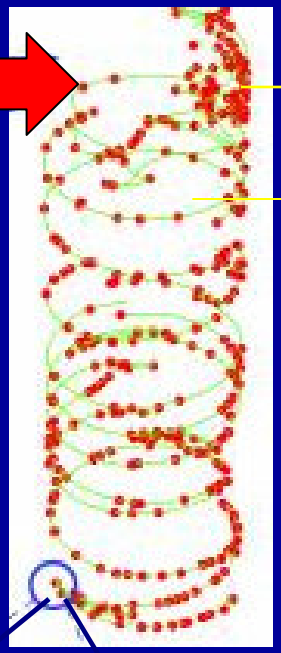




Better models of behaviors

Extensive automated behavioral analysis

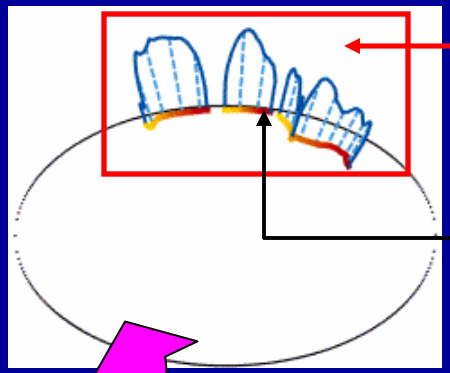




The path in a 3D representation of X, Y, and time

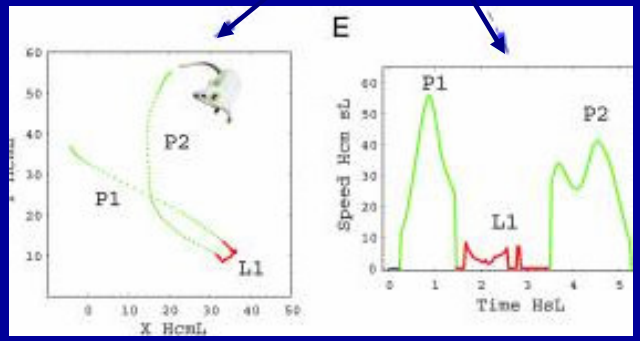
Slow movement episodes (e.g., stops)

Progressions (green)



New approach: sensitive to stress, drugs and genetic differences

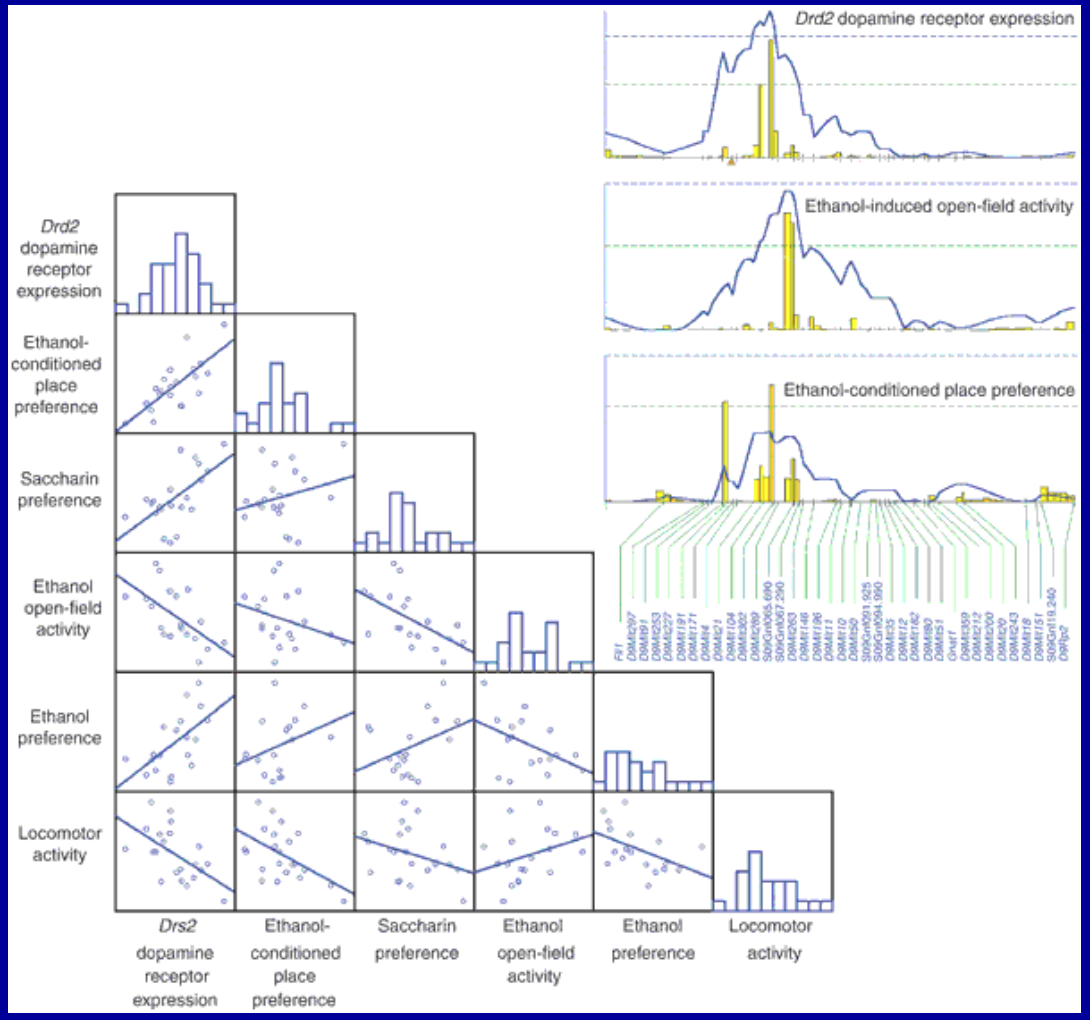
Traditional approach



The path plot and speed profile of two progression segments (P1 and P2) are separated by one “stopping” episode

Kafkafi et al., 2005, PNAS

Gene-Behavior correlations

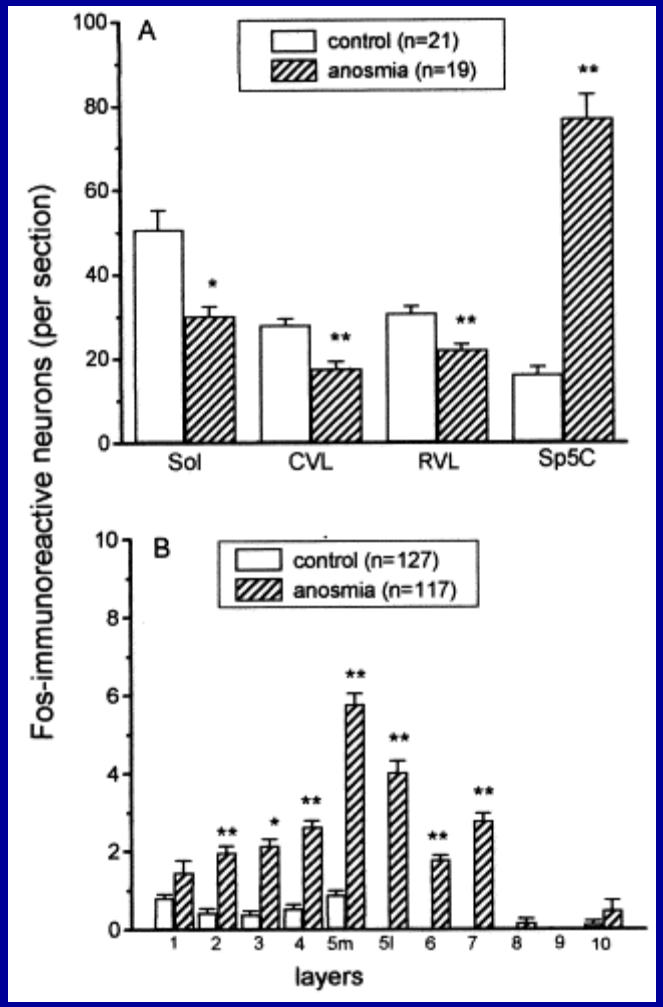


Correlation of *Drd2* expression (MA)

with several behavioral phenotypes

Chesler et al., 2005

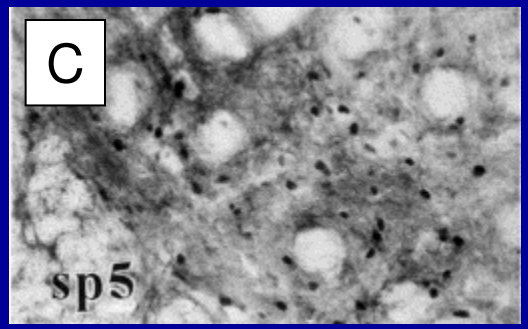
Functional neurogenomics: c-fos

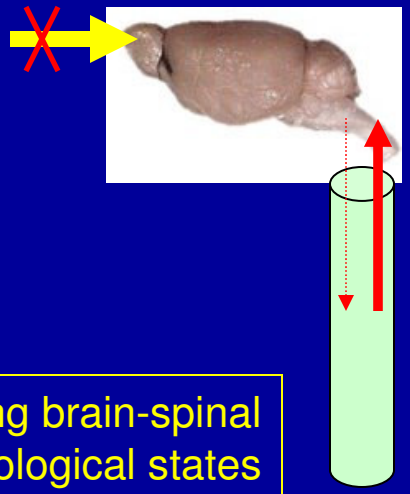


A: Number of Fos-LI cells in the nucleus of solitary tract (Sol), caudal and rostral parts of ventrolateral medulla (CVL, RVL) and the spinal trigeminal nucleus caudalis (Sp5C) in anosmic vs. control rats

B: Number of Fos-LI neurons in different layers of the lumbar enlargement (L4/L5) in anosmic vs. control rats

C: Intensive Fos-immunoreactivy in the spinal trigeminal nucleus caudalis in anosmic rat

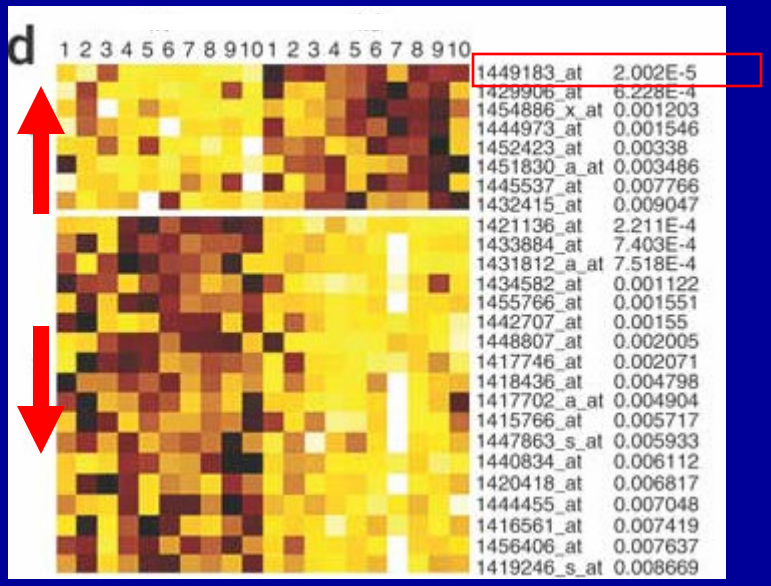




May be relevant to modeling brain-spinal networks at different physiological states

Kalueff et al., 2001, Neurosci Lett

Functional neurogenomics: MA



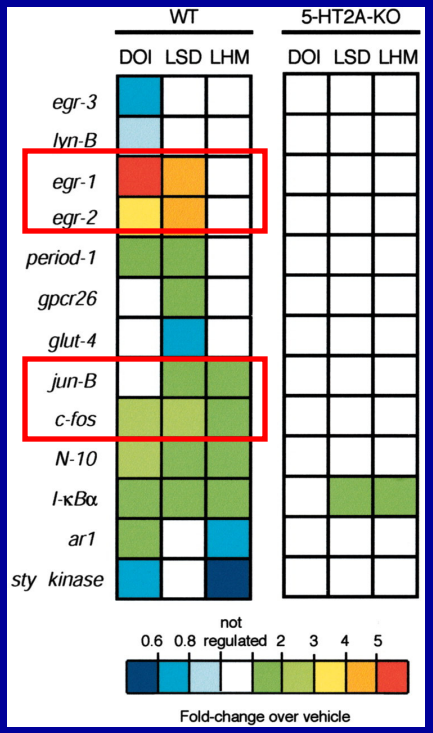
Paterlini et al., 2005, Nat Neurosci

Schizophrenia-related phenotype in *Prodh* knock-down mice associated with up-regulation of cateholamine-O-methyl-transpherase (COMP) gene in the cortex

G x G

Drug x G

Early genes

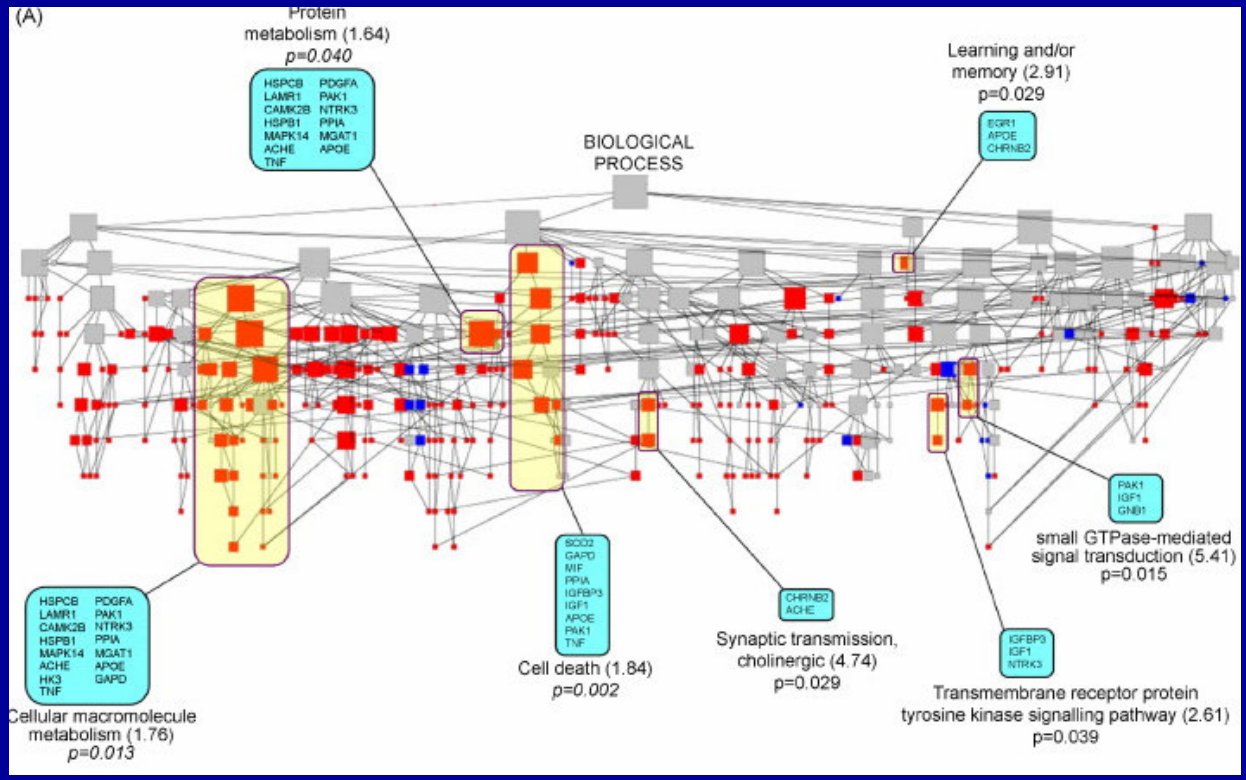


Transcriptome fingerprints induced by 5-HT2AR agonists
In wild-type (WT) and 5-HT2AR null-mutant (KO) mice

Gonzales-Maeso et al., 2003, J Neurosci

High-throughput “omics”: functional gene networks

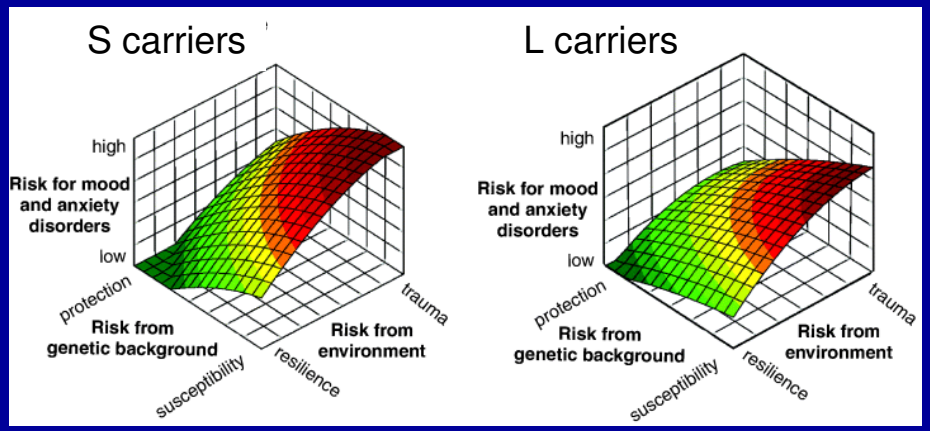
32 genes differentially expressed in mice-winners and losers (GoMiner). GoMiner classified these genes into biologically coherent categories and assessed these categories, generating hypotheses on how these genes may be related

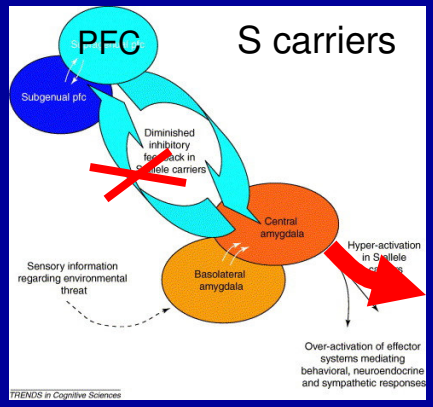


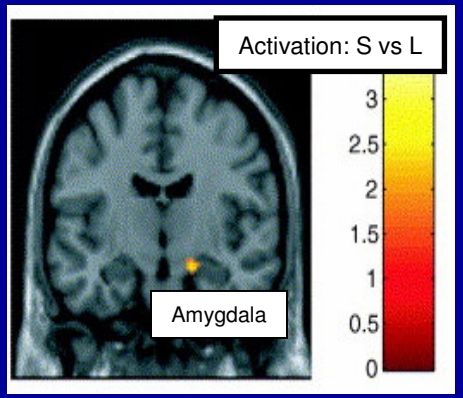
Kroes et al., 2007, Behav Brain Res, in press

Modeling genetics of brain disorders

3D model of SERT contribution to individual differences in negative emotionality, mood and anxiety disorders

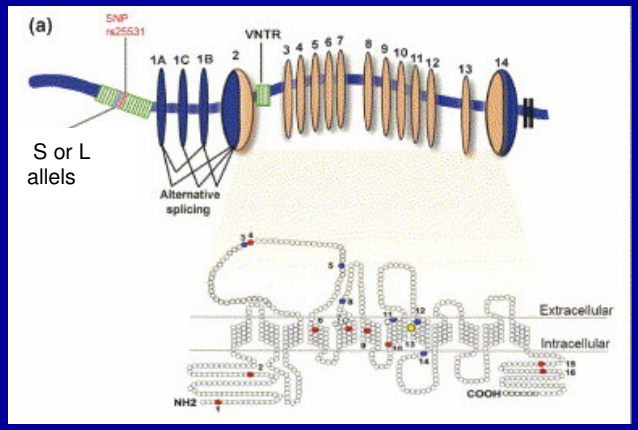


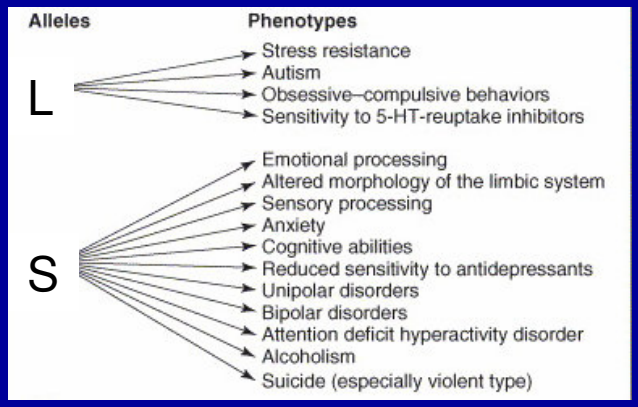




Holmes and Hariri, 2003, 2005

Human SERT genetic polymorphisms and neuropsychiatric phenotypes

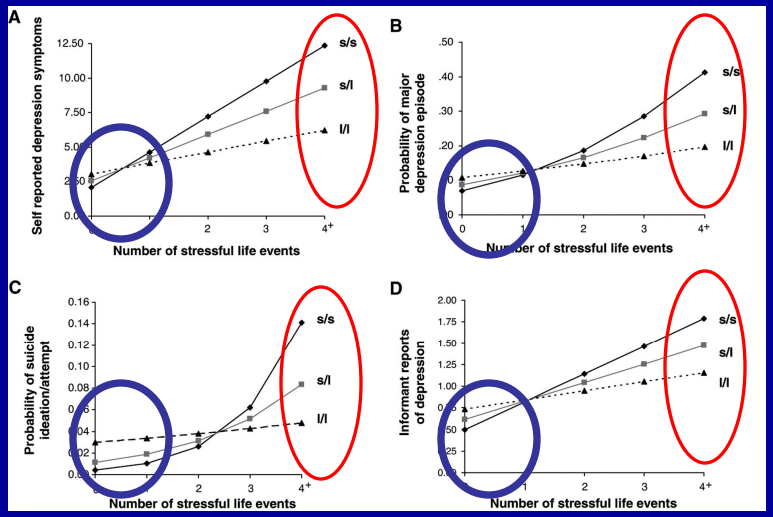




Kalueff et al., 2007

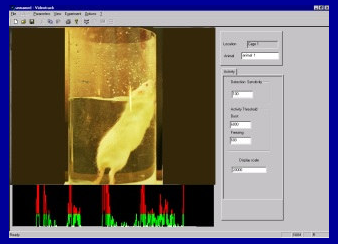
Modeling complex brain phenotypes: G x E

Gene x environment interactions: SERT gene variants and clinical depression



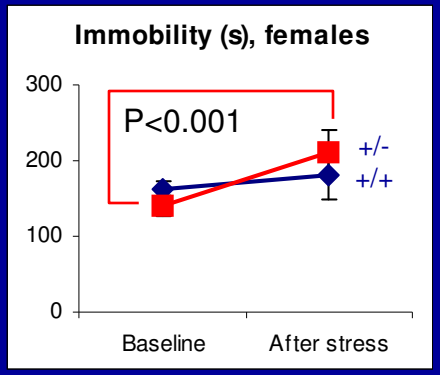
Caspi et al., 2003, Science

Replication of Caspi's study in SERT+/- mice using the forced swim test (immobility = despair)

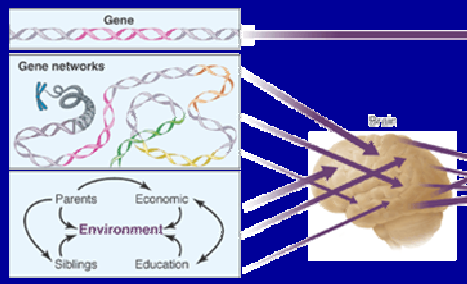


The forced swim test

SERT+/+ mice = l/l
SERT+/- mice = s/s or s/l



Kalueff et al., unpublished data



Behavior

Behavior

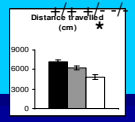
Hammer D, 2002, Science

The importance of modeling neural x gene x environment networks

Building phenotype networks: SERT-/- mice

Kalueff et al., CINP, 2007

Hypoactivity



Aberrant brain development

Esaki et al.,2002

Serotonin + Rs dysregulations

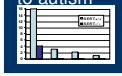
Low aggression
[Holmes et al., 2003]

Obesity

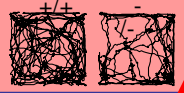
+/+ +/- -/-

May be relevant to human eating disorders and OCD

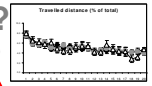
Social deficits
May be relevant to autism



Anxiety



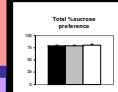
Memory, learning? Other cognitions?



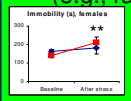
Reward
[Hall et al., 2002]

Straub tail

No anhedonia

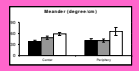


Vulnerability to severe chronic stress
(e.g., rat exposure

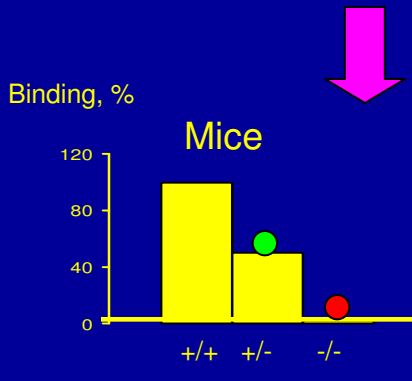


Serotonin syndrome-like phenotype
[also see Fox, Murphy, 2006]

Stereotypic turning and meandering

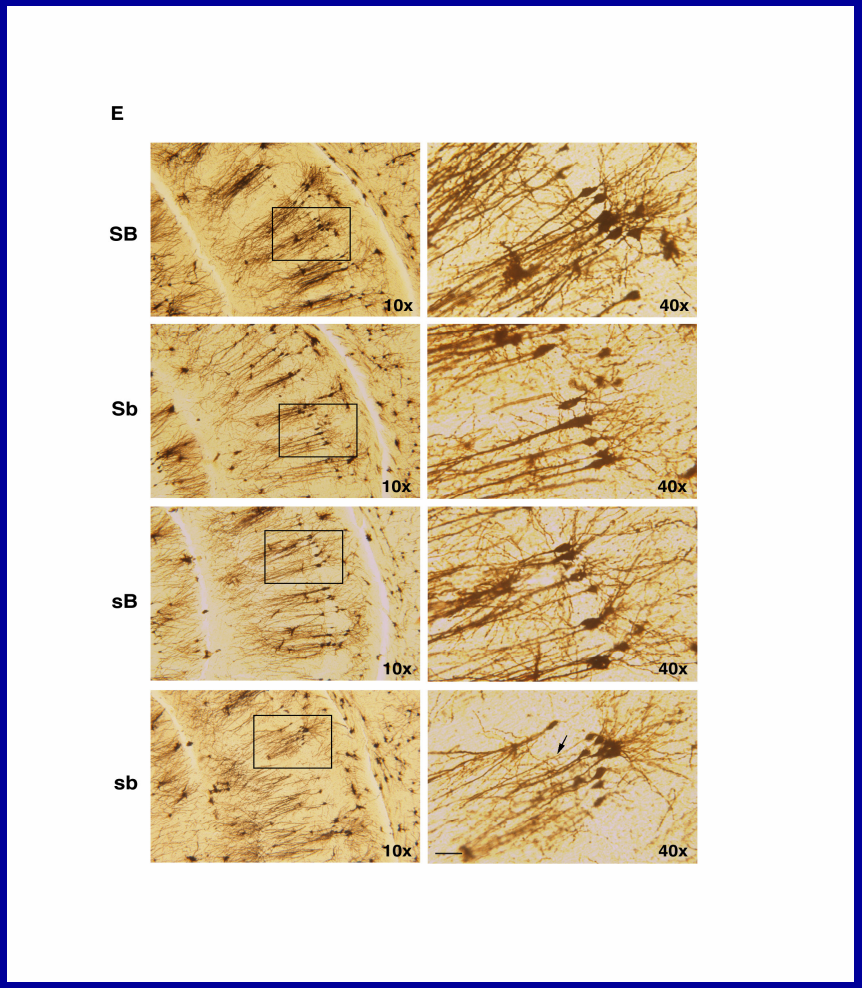


May be relevant to OCD or autism



Translating animal phenotypes into human behavior

Gene x Gene interactions: gene networks



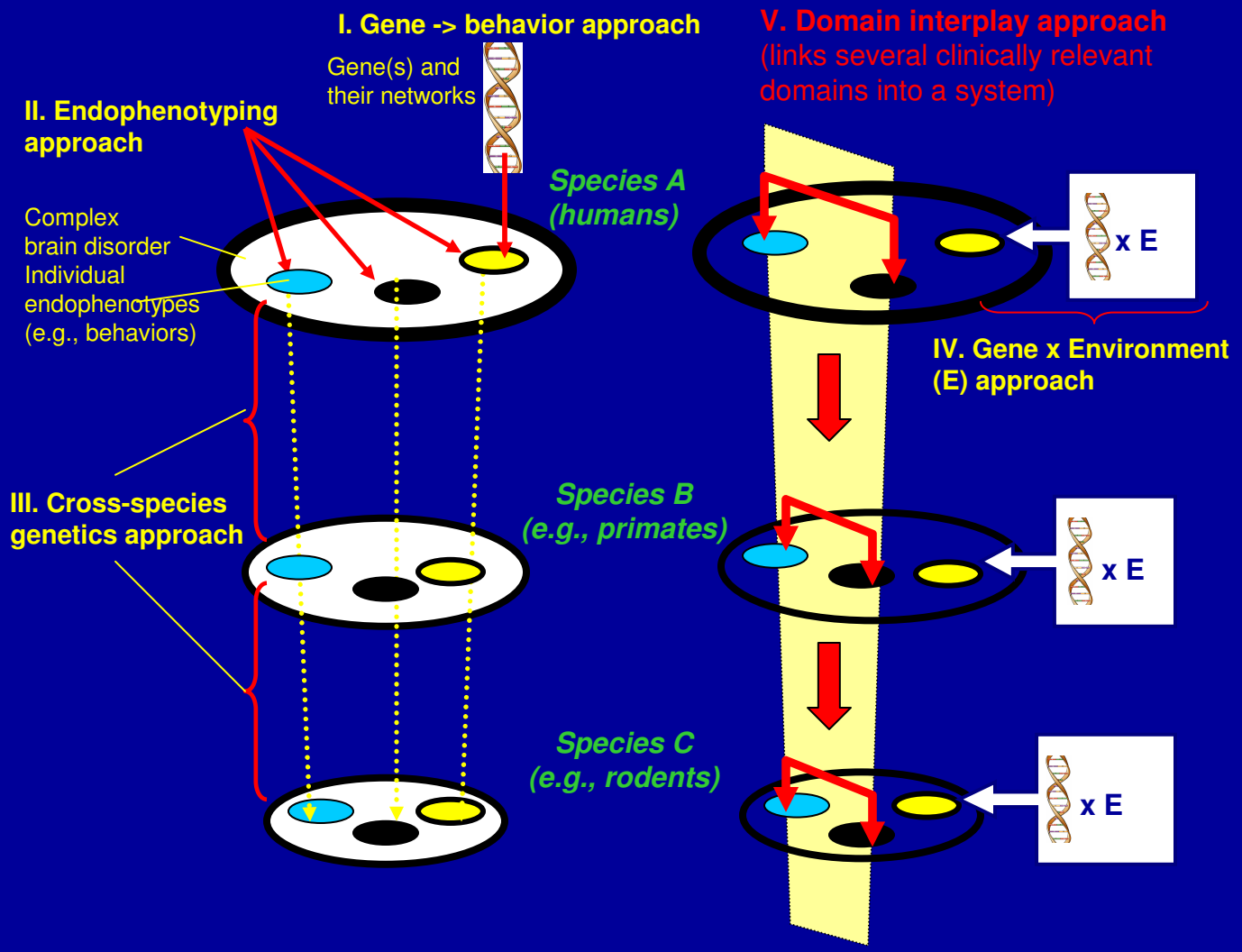
SERT-/- x BDNF+/- mice

Exaggerated anxiety in SERT-/- x BDNF+/- mice (Ren-Patterson et al., 2005)

Altered neuronal morphology and neurochemistry in SERT-/- x BDNF+/- mice (Ren-Patterson et al., 2005)

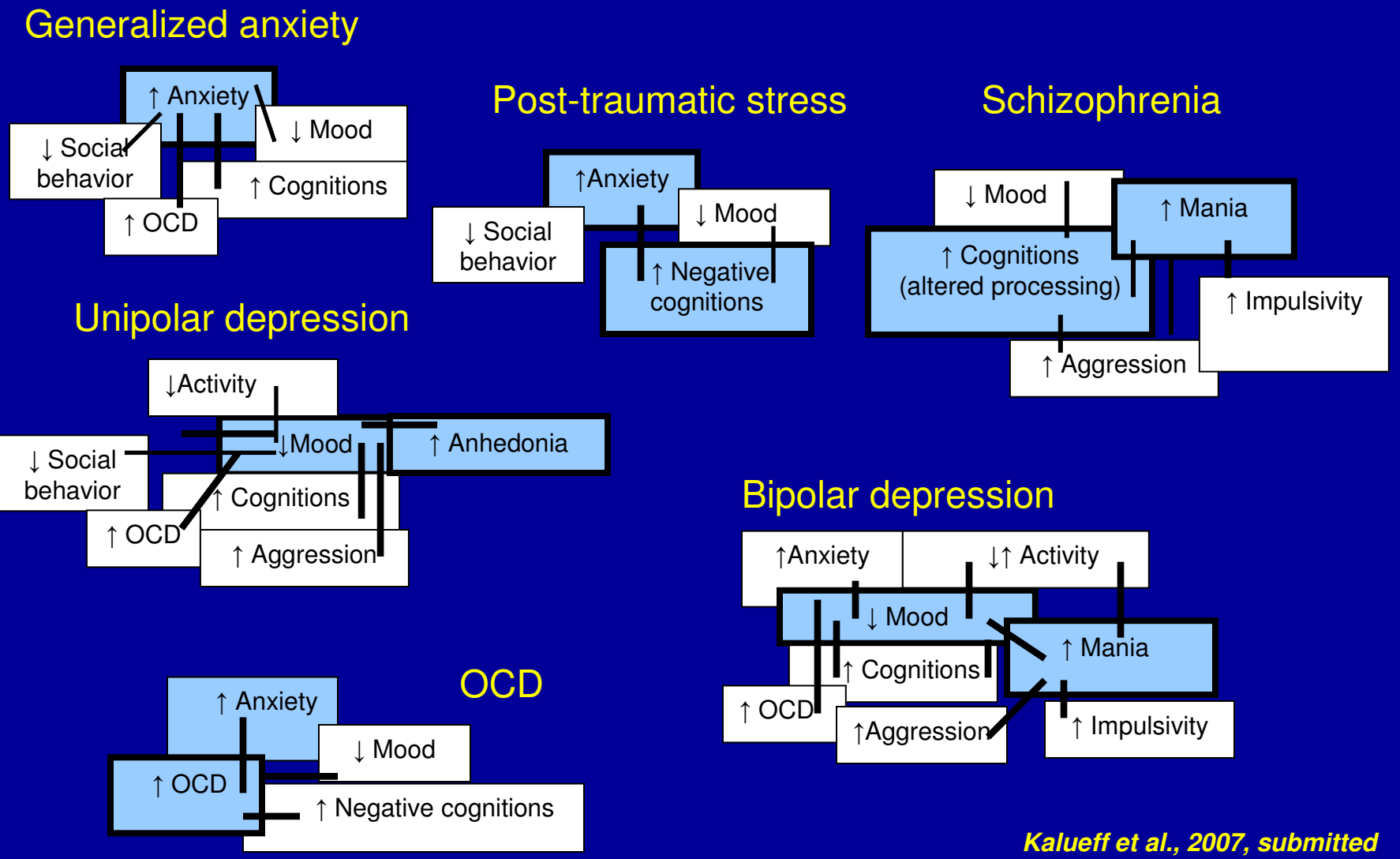
Ren-Patterson et al., 2005, J Neurosci Res

Modeling domain interplay in biopsychiatry



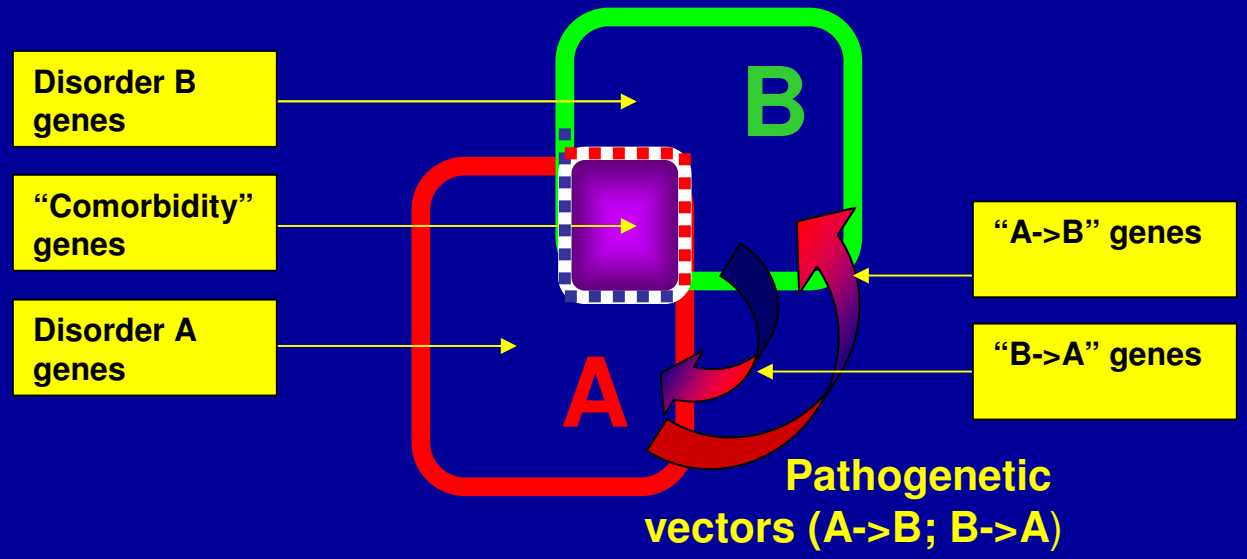
Kalueff et al., 2007, submitted

Domain-oriented modeling of brain disorders



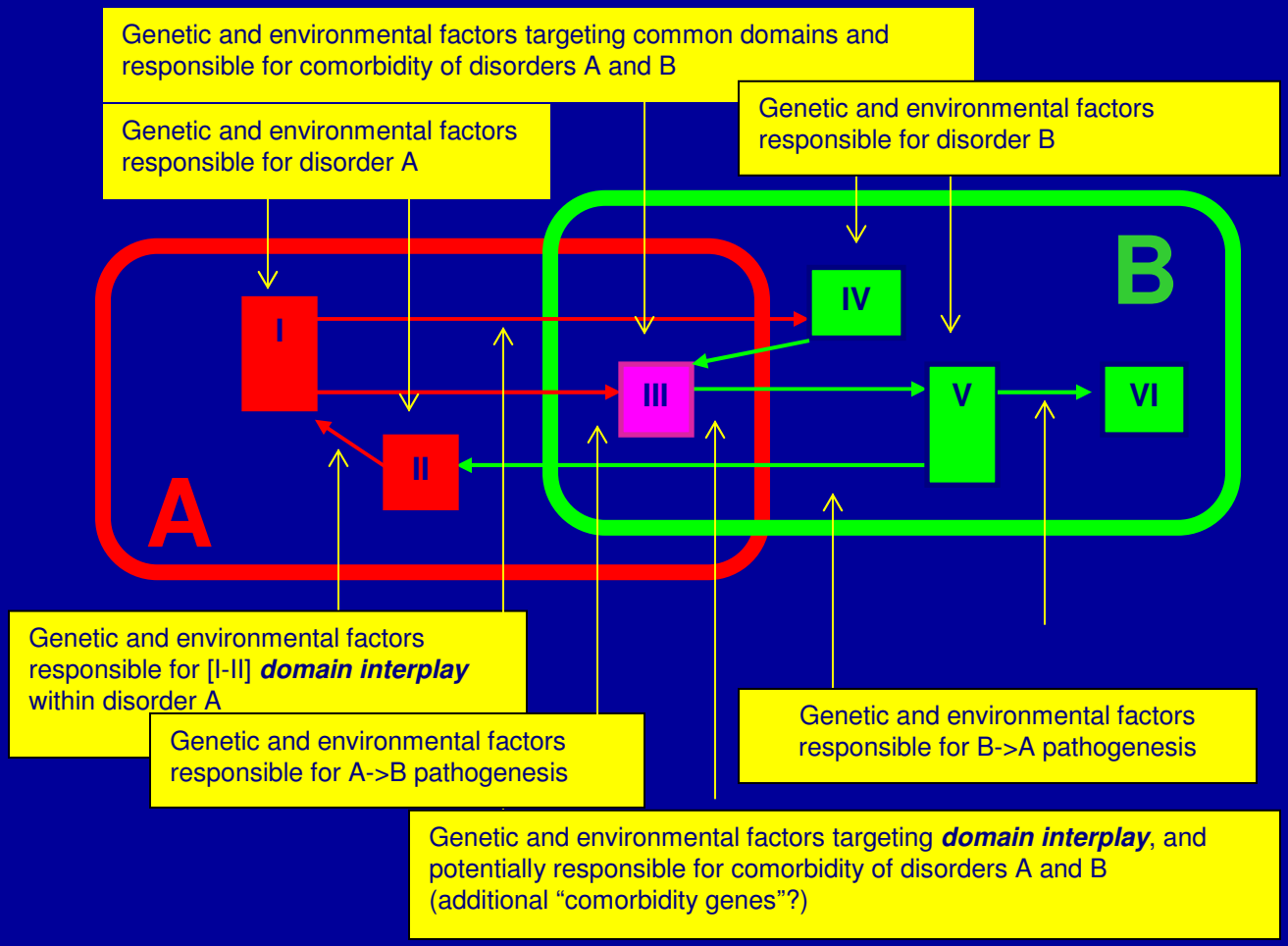
Kalueff et al., 2007, submitted

Domain-oriented modeling of brain disorders



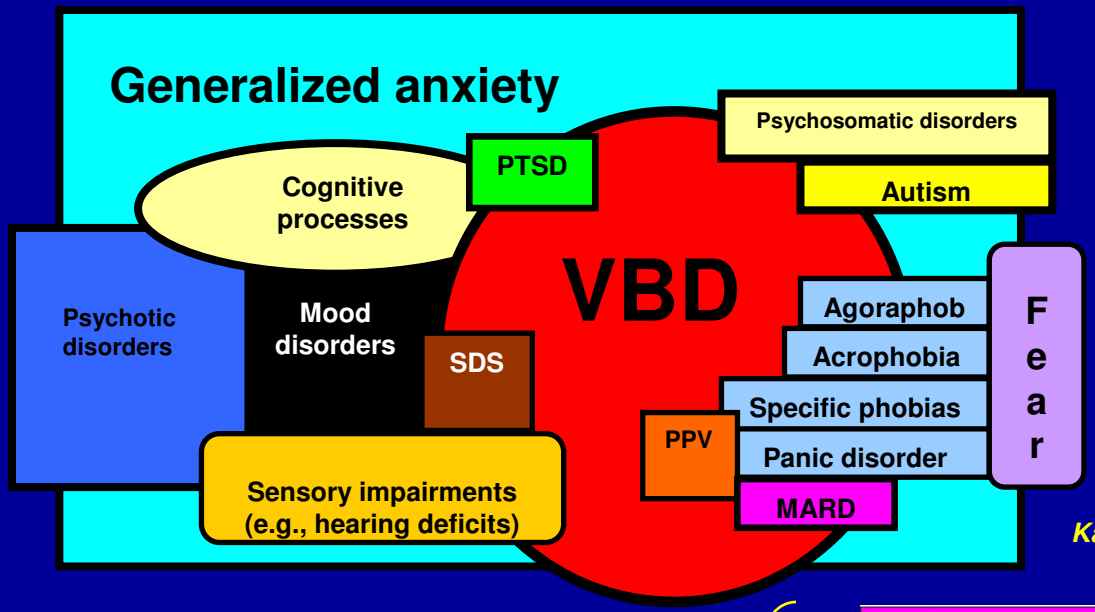
Kalueff et al., 2008

Domain-oriented modeling of brain disorders



Kalueff et al., 2007, submitted

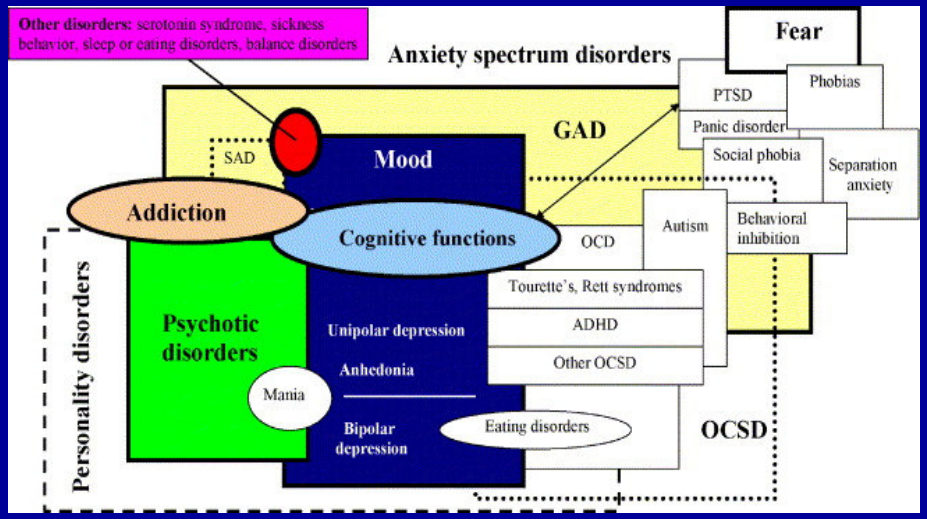
Domain-oriented modeling of brain disorders



Anxiety, vestibular functions and sensory-motor integration

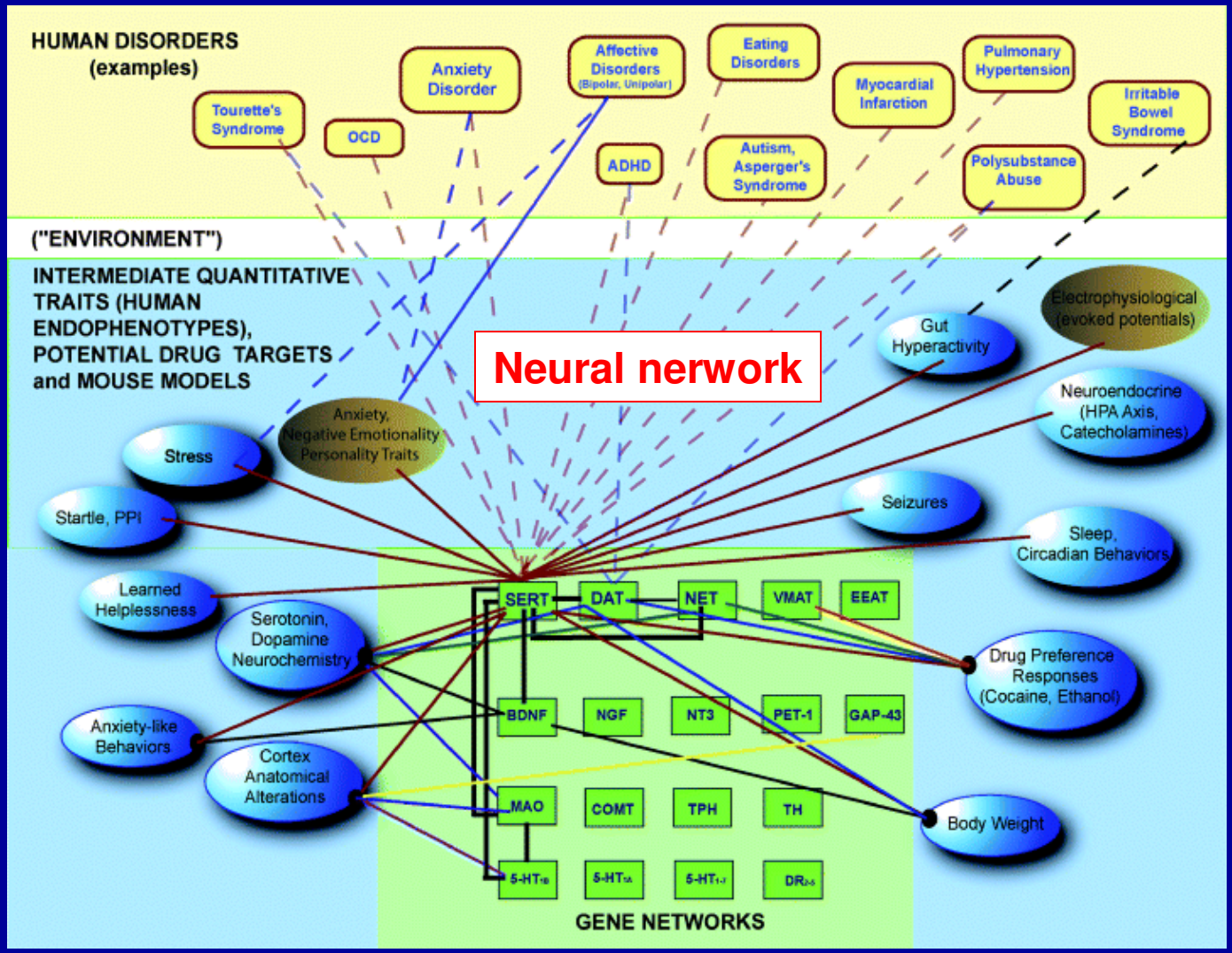
Kalueff et al., 2007, Bevavioral Brain Research, in press

Continuum nature of neurobehavioral disorders



Kalueff et al., 2007, Bevavioral Brain Research

Network-based modeling of brain disorders



Murphy et al., 2003

Other interesting topics for QNP

- Molecular modeling of brain receptors
- QTL and behavior
- Information theory: applications to brain mechanisms and behavior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"...then we add a smidgin of this - that's less than a dollop, but more than a pinch... "