Modeling Domain Interplay

1st ISBS Summer School

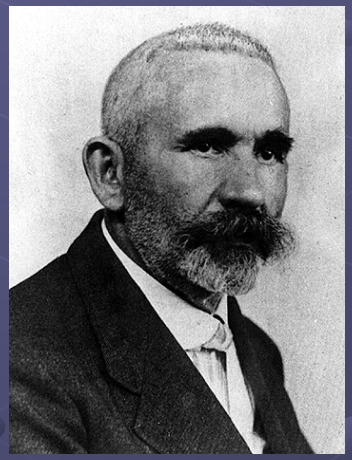
St. Petersburg, Russia

May 9th -15th,2008

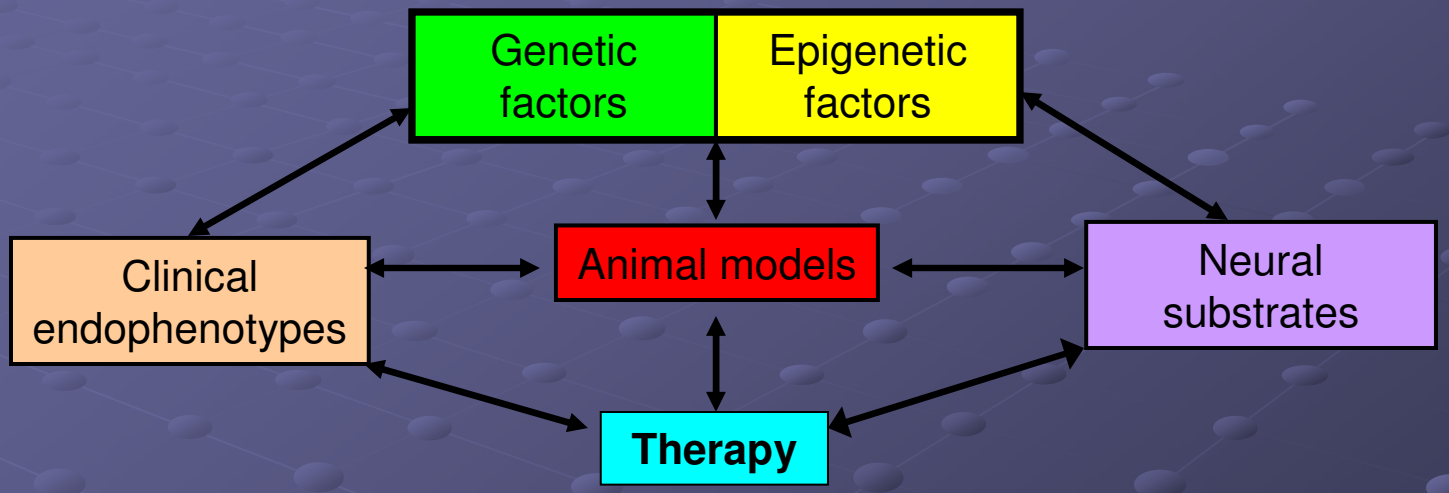
Mouse psychiatry.

Do we need it?

[once we already have such complicated "human" psychiatry?]



Animal models in biological psychiatry

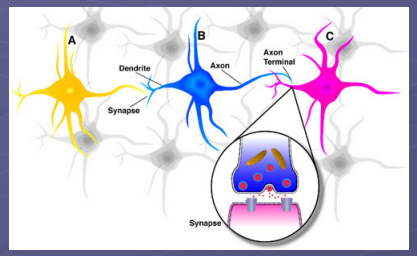


- Dissect neural circuits of brain pathology
- Identify candidate genes
- Model the effects of stress and other environmental factors
- Screening of new drugs and other manipulations

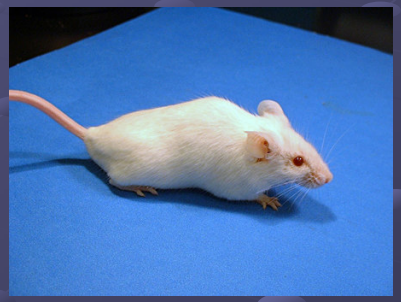
Neurophenotyping approach

Neurons

Neural networks

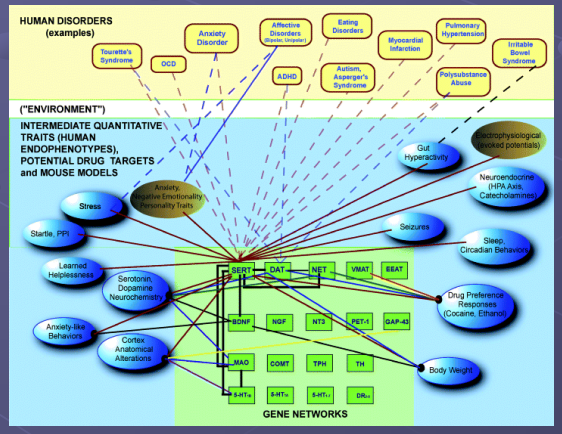


Complex behaviors



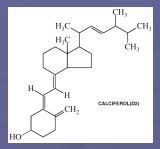
Translating animal behavior into complex human phenotypes

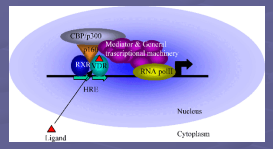
Models of human brain disorders



Murphy et al., 2003

Step-by-step phenotyping approach

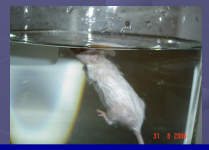




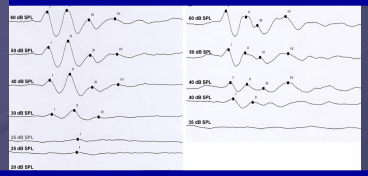
- Vitamin D is a steroid hormone
- Has multiple functions in the CNS
- Acts via nuclear receptors (VDR)

VDR-/- mice

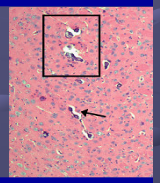
Aberrant swim

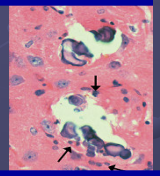


ABR waves +/+ -/-

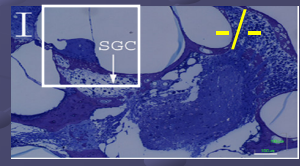


Thalamic calcification

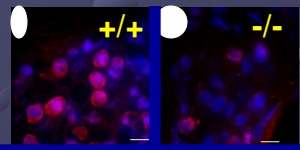




Spiral ganglion cell loss



Caspase 3 activation



1997 2003 2004 2005-2006 2007

Kato et al.
Generation of the mouse

Kalueff et al.
Increased anxiety
Cited>30 times

Kalueff et al.
Impaired swimming

Kalueff and Bart:
Hearing loss

Kalueff et al.
Thalamic calcification

Zou, Kalueff et al. (in press)
Aberrant inner ear morphology,
reduced caspase 3 activation

Single domain oriented models can be helpful in biomedical research

Current phenotyping strategies

Environment

Behavior:
G x B
G x E

Endophenotype 1
Endophenotype 2
…
Endophenotype n

Simplifying behavior:
ENDOPHENOTYPES

Cross-species trait genetics

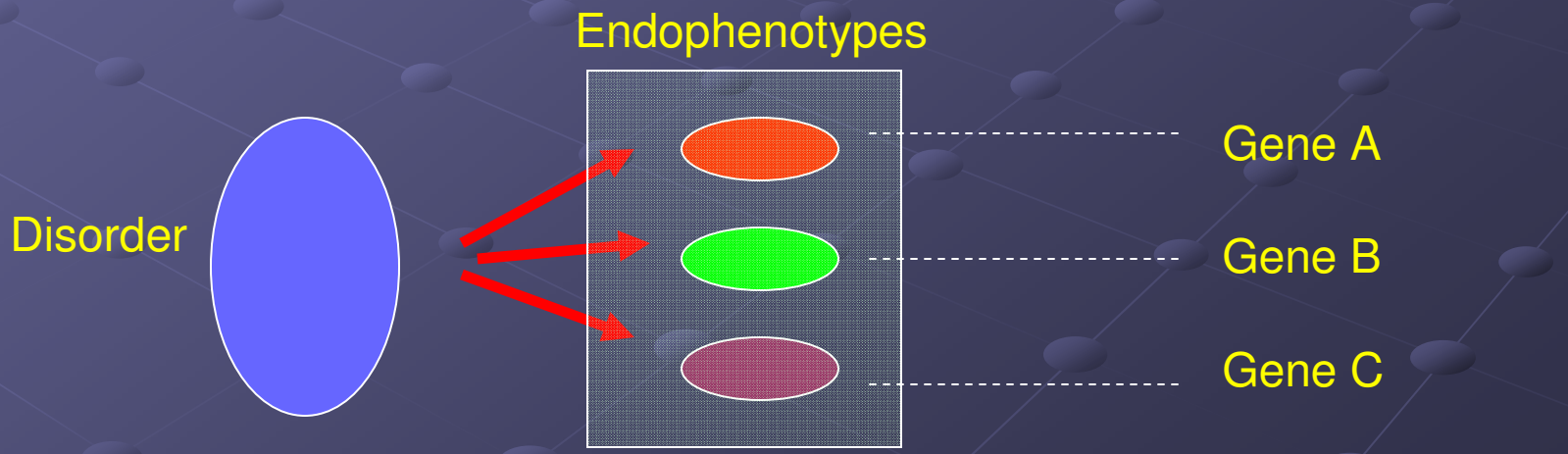
Endophenotypes

An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature.

Endophenotypes represent simpler clues to genetic underpinnings than the disease syndrome itself

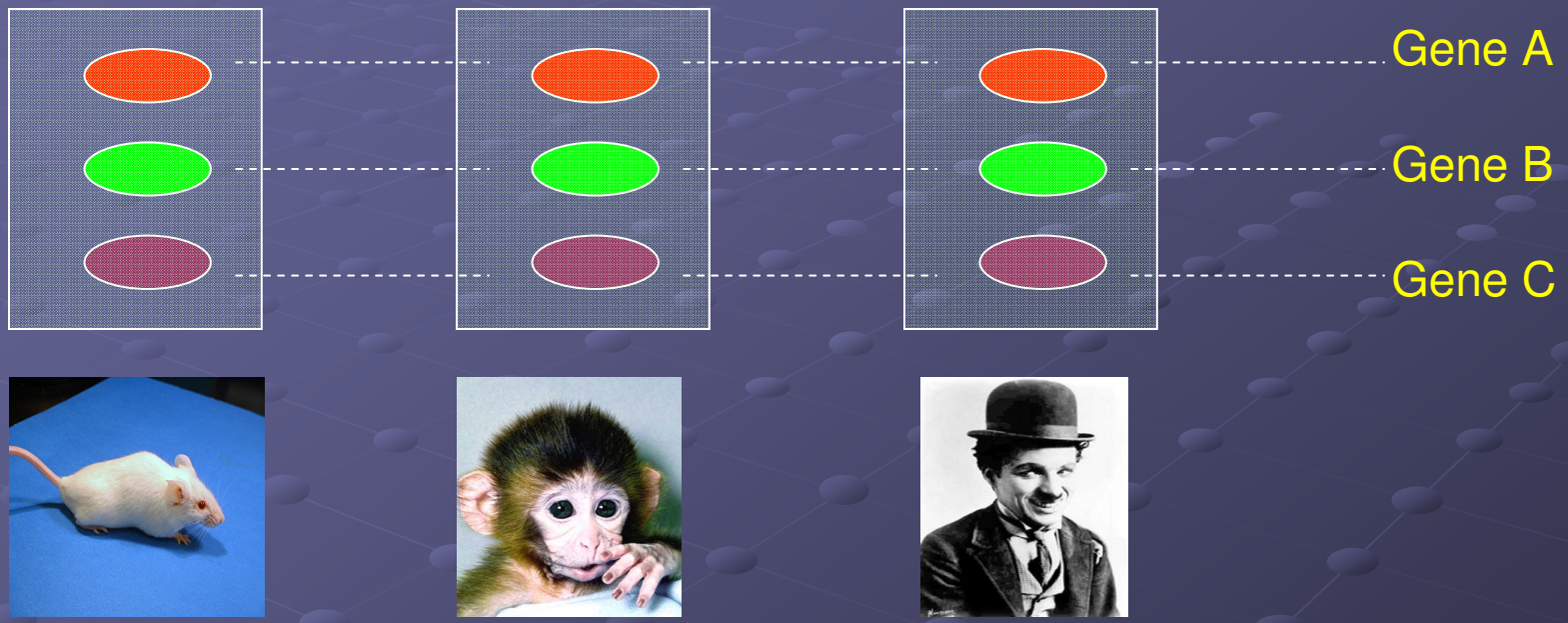
They promote the view that psychiatric diagnoses can be decomposed or deconstructed, which can result in more straightforward—and successful—genetic analysis.

Gould, Gottesman, 2003



Cross-species trait genetics

Kas et al., 2007, Mol Psychiatry



Pitfalls:

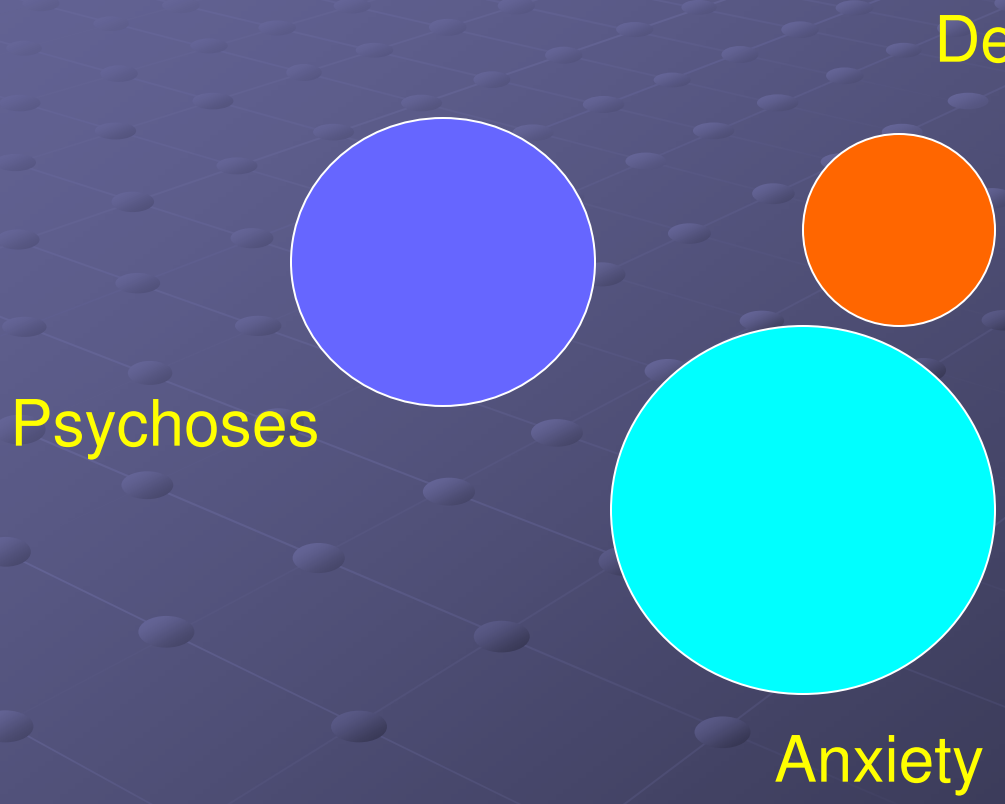
Not all behaviors are analogous in mice and men

Not all human endophenotypes are properly understood

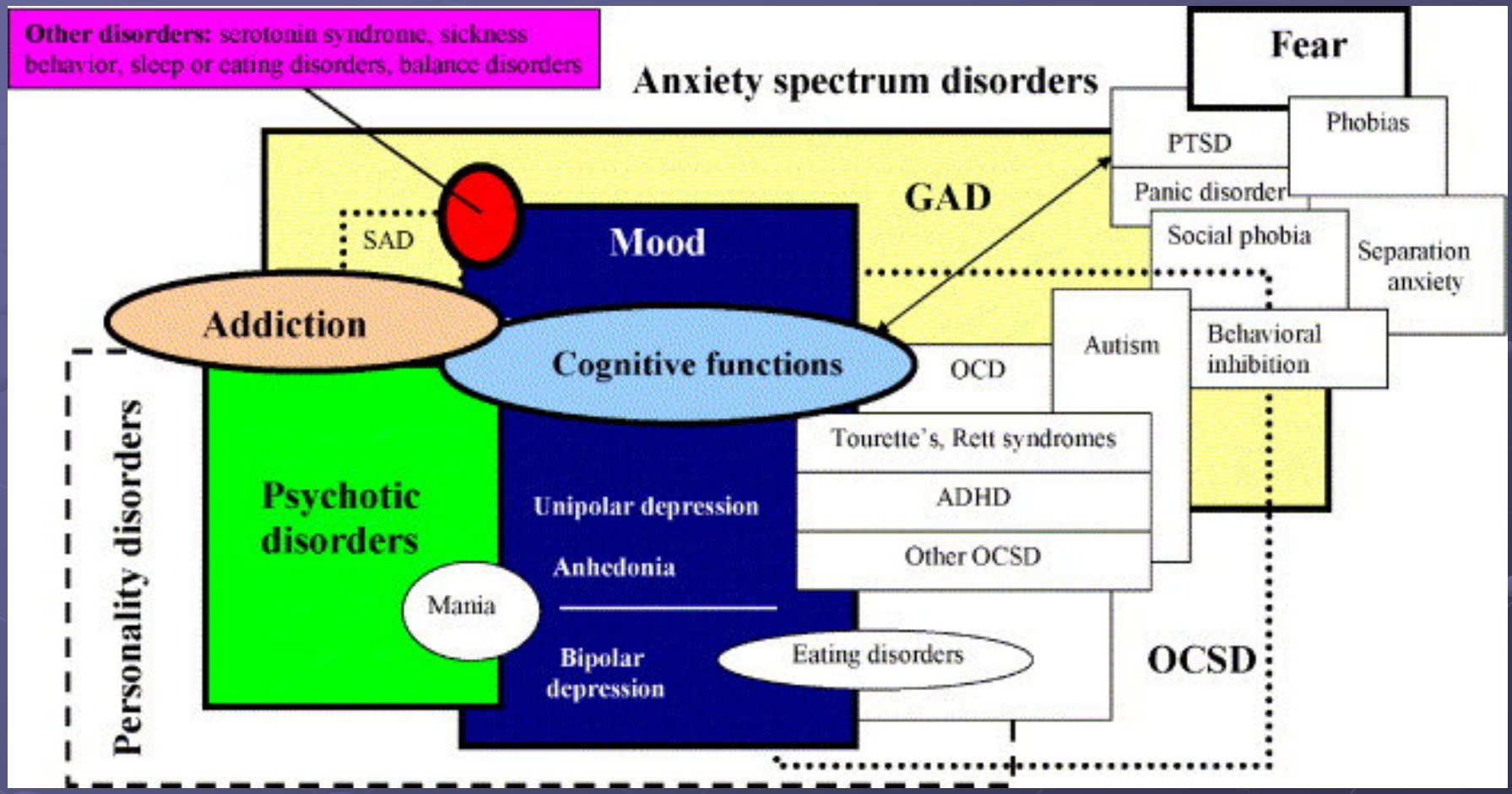
Not all genes are homologous in mice and men

Disorder-related phenomena frequently overlap

“Ideal” psychiatry

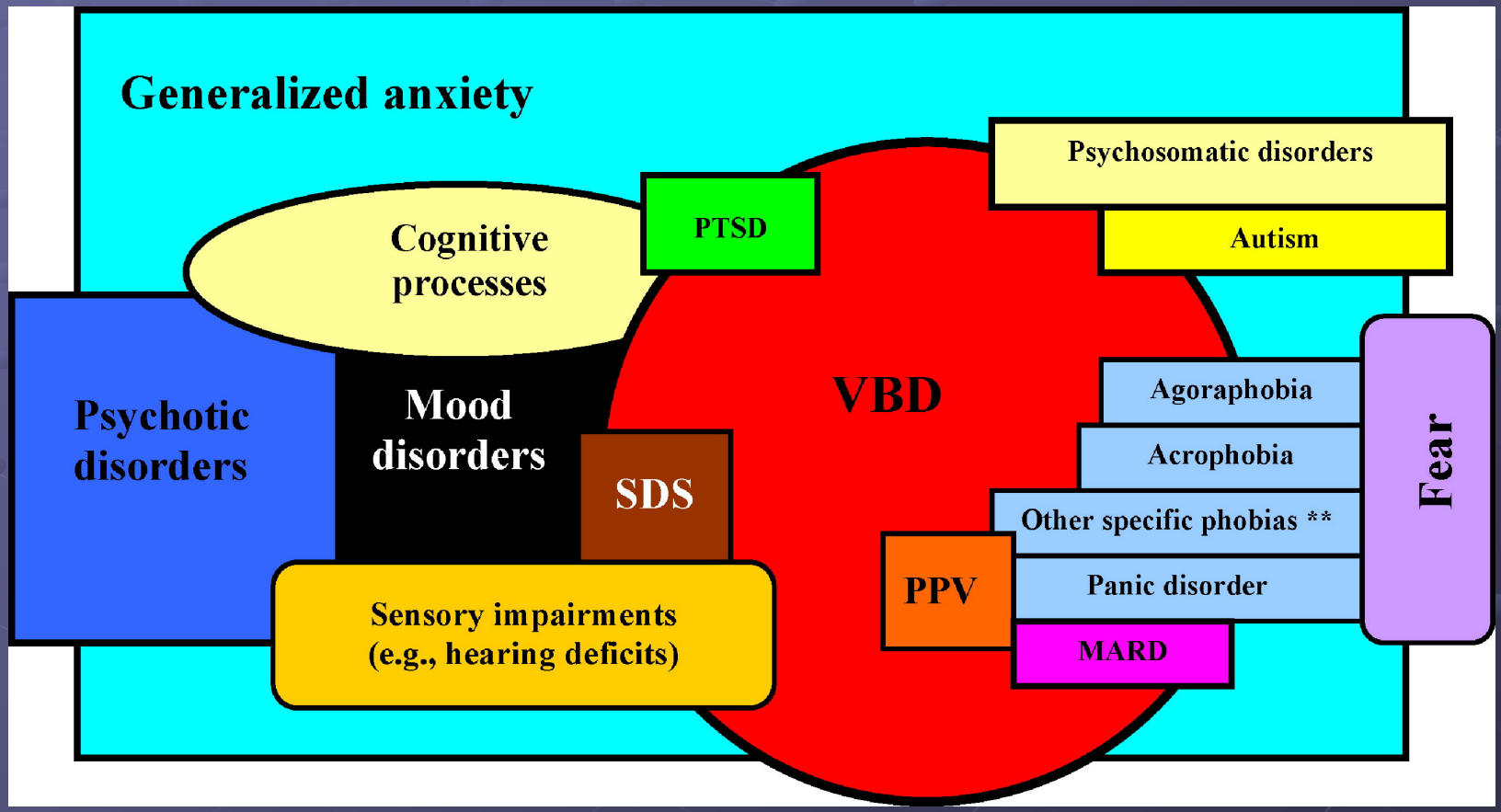


“Real” psychiatry



Kalueff et al., 2008, Behav Brain Res

“Real” psychiatry



Problems with current animal models

Mostly single-domain oriented

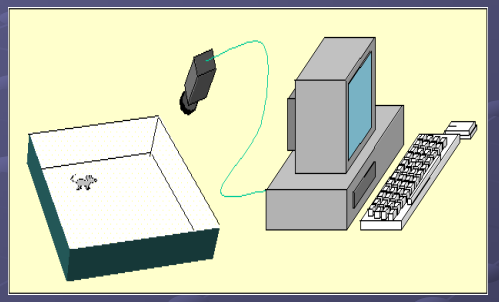
Lack of fresh ideas (“old and boring”)

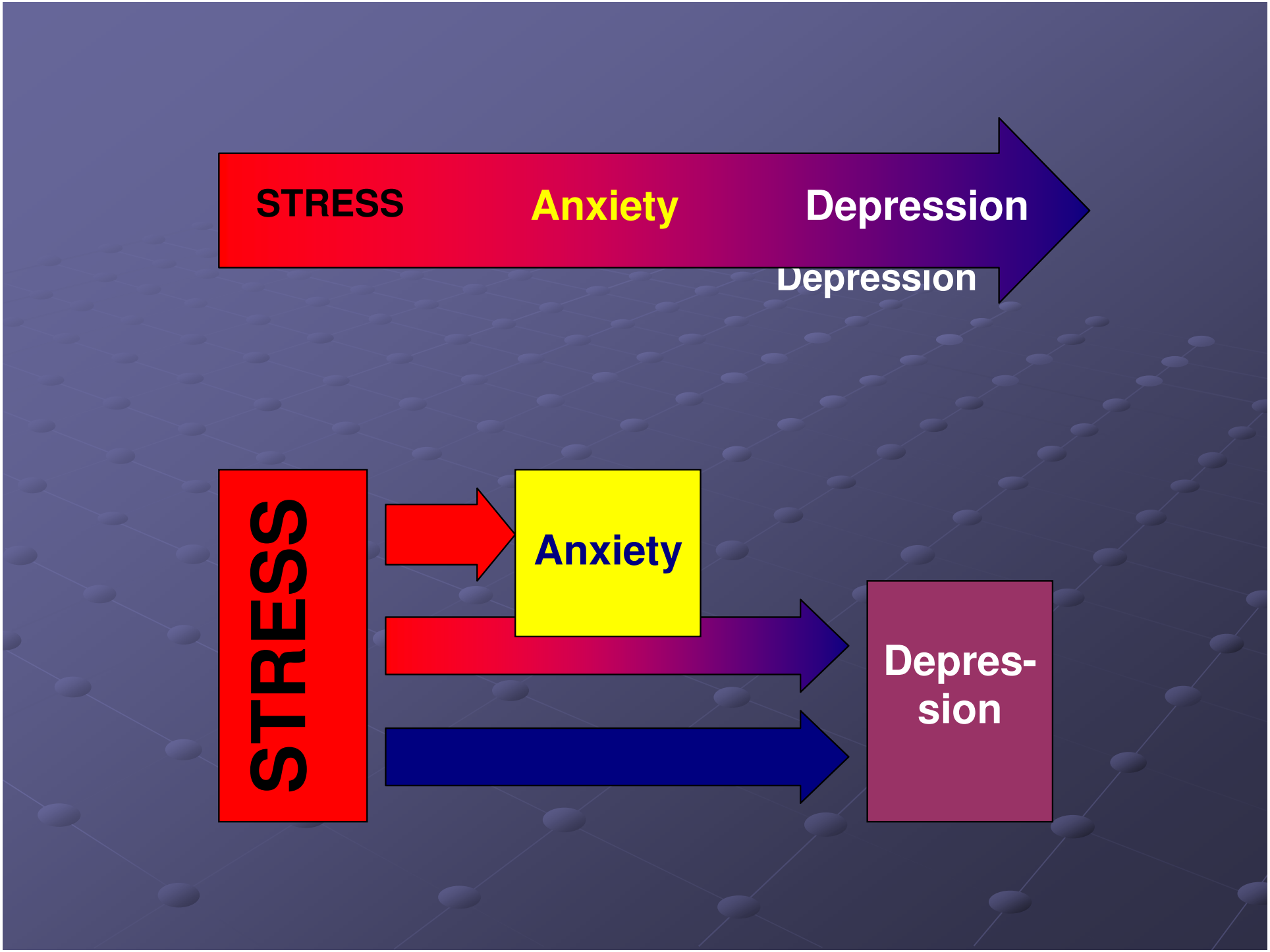
Target major constructs (e.g., GAD, MDD) but not subtypes of disorders

Do not address “spectrum” nature of pathogenesis

Do not reflect co-morbidity aspects

Lagging behind constantly changing clinical diagnostic criteria




STRESS
Anxiety
Depression
Depression
STRESS
Anxiety
Depres-
sion

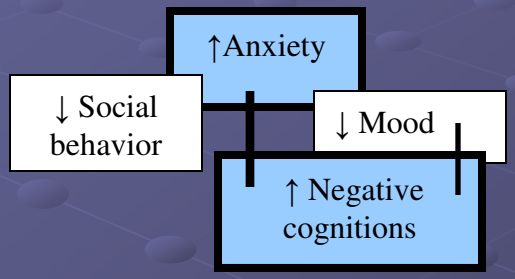
We need new approaches to modeling neuropsychiatric disorders

Domain interplay concept

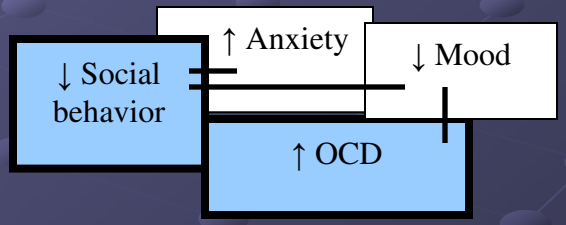
Kalueff et al., 2008, Behav Brain Res

In addition to focusing on individual phenotypes, we need to focus on clinically known interplay between domains (endophenotypes)

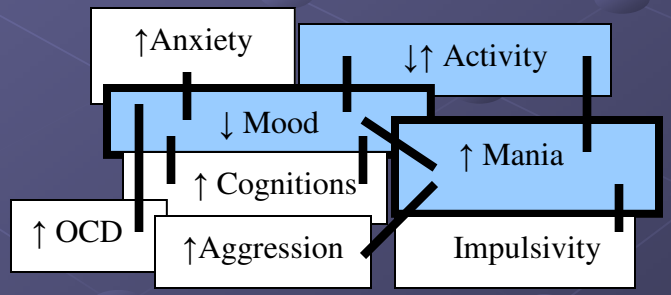
Post-traumatic stress disorder



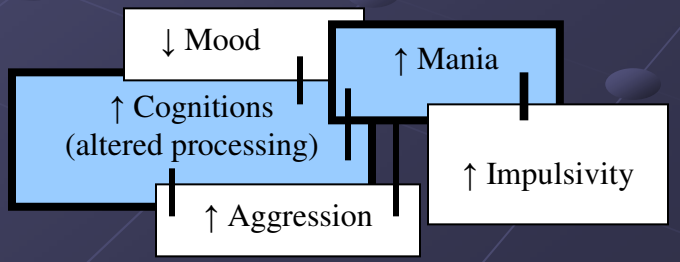
Autism



Bipolar depression



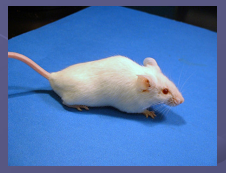
Schizophrenia

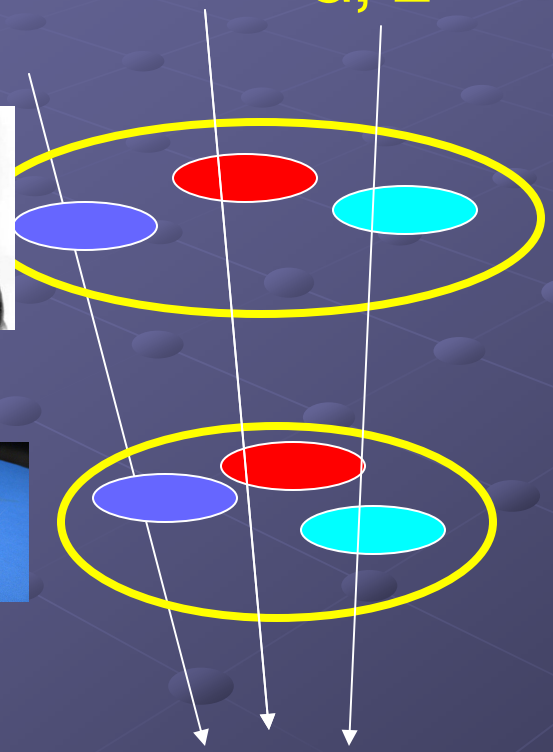


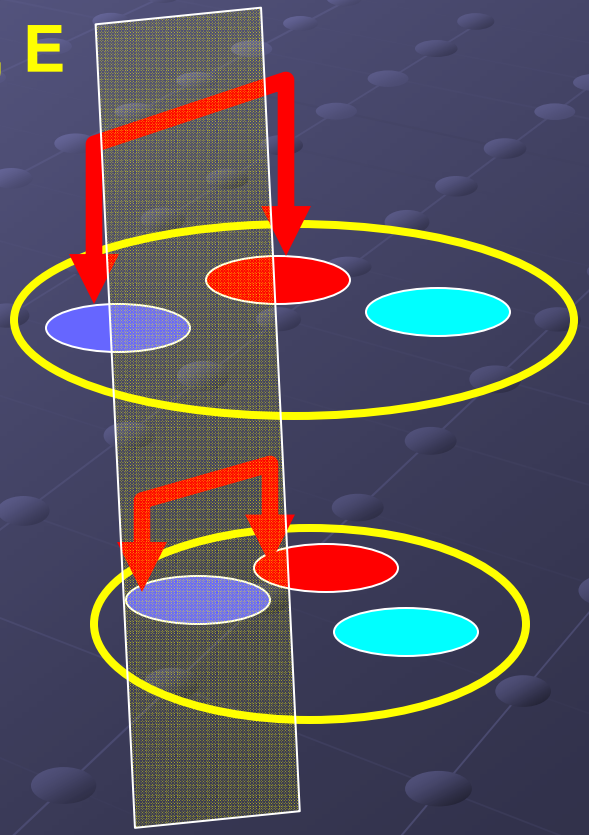
Domain interplay concept

Kalueff et al., 2008, Behav Brain Res

Instead of viewing endophenotypes as static “points”, we can focus on SYSTEMS of interplaying phenotypes

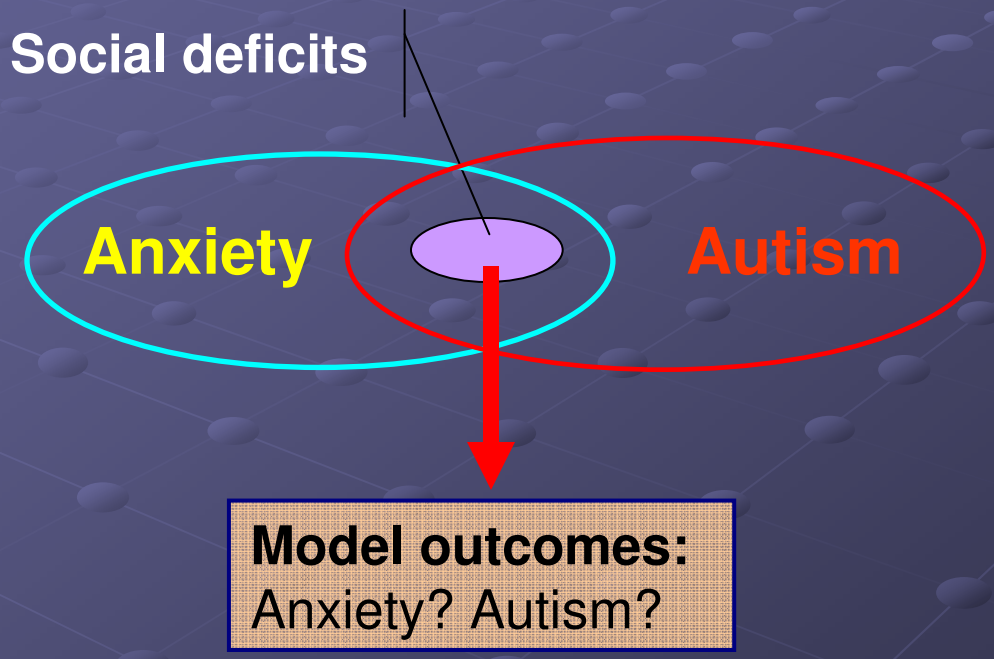






Domain interplay concept

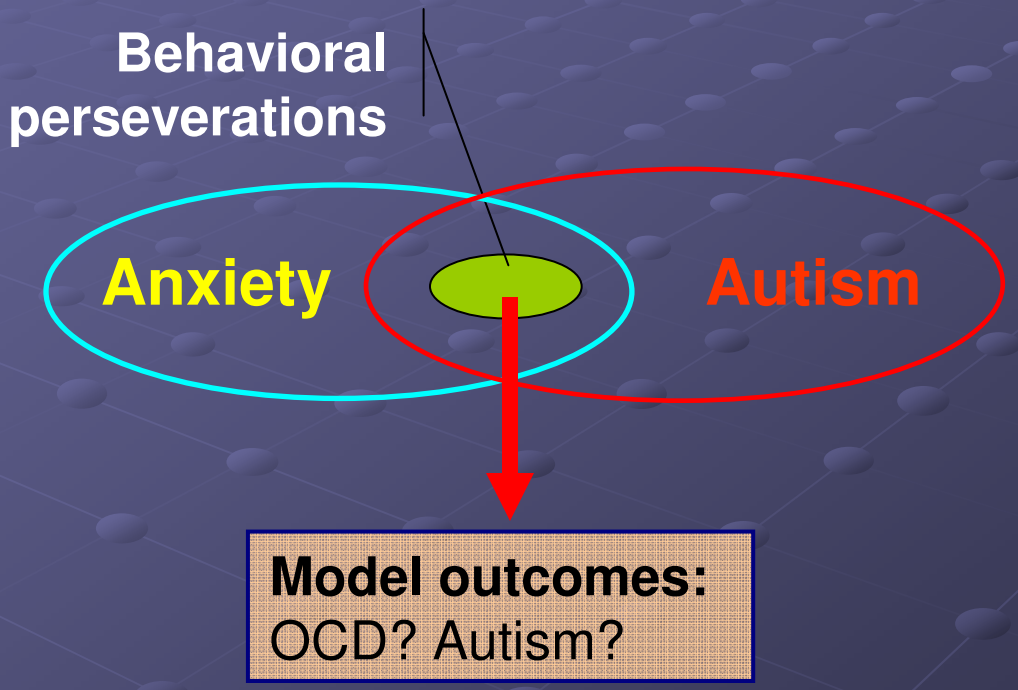
Focus on a single domain in a mouse model



Kalueff et al., 2008, Behav Brain Res

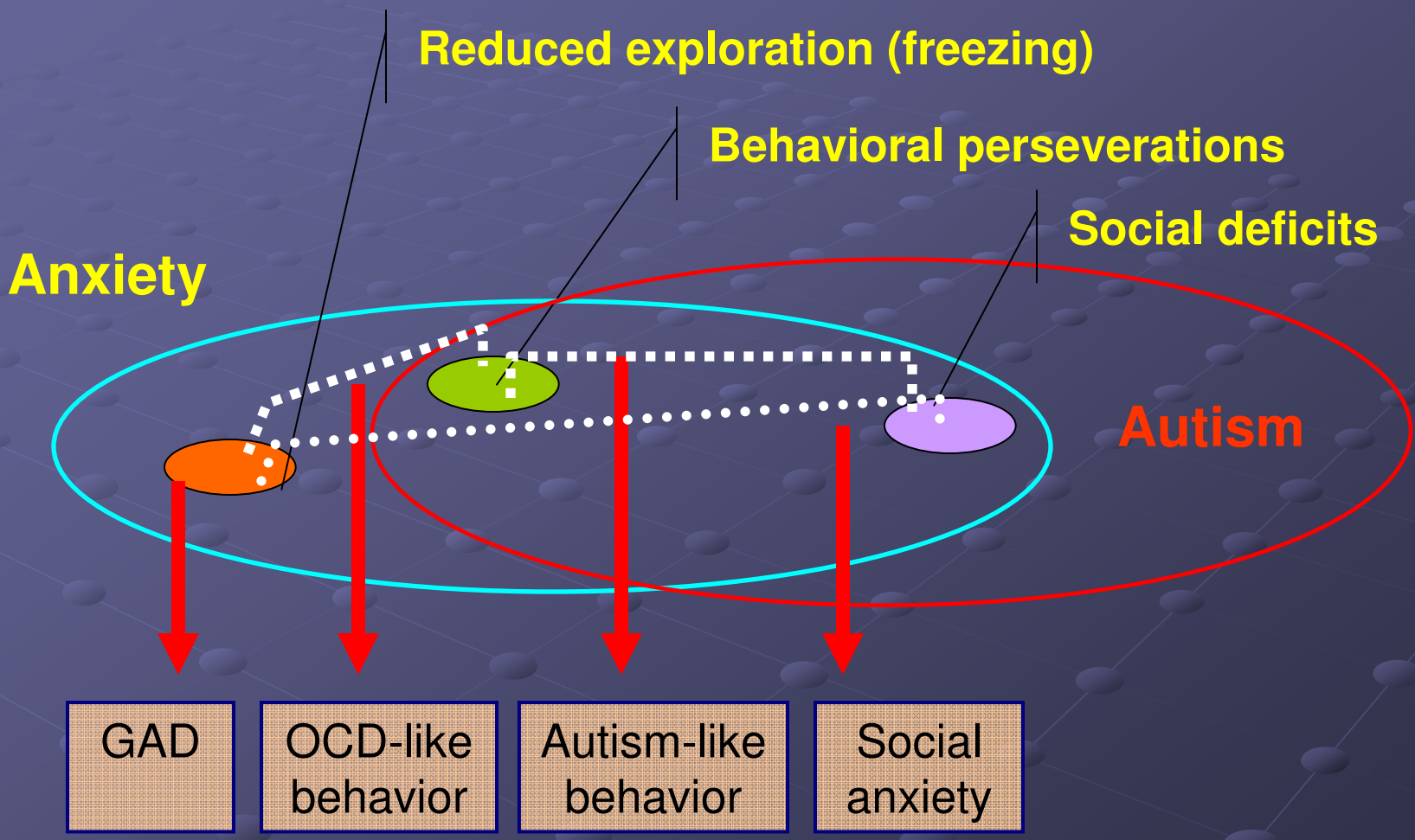
Domain interplay concept

Focus on a single domain in a mouse model



Kalueff et al., 2008, Behav Brain Res

Focus on a system of interplaying domains

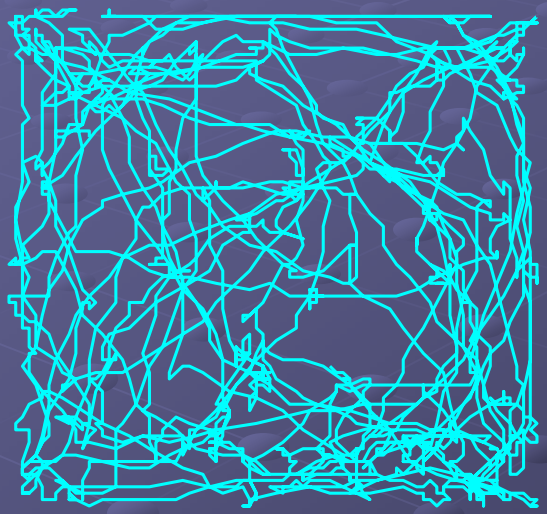


Kalueff et al., 2008, Behav Brain Res

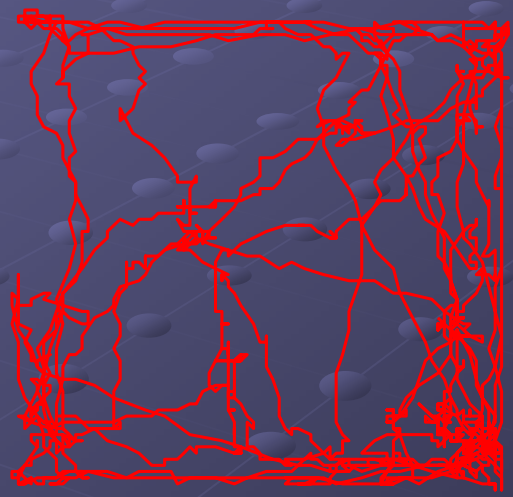
Example: SERT-/- mice

Activity in novel cage

+/+ mice

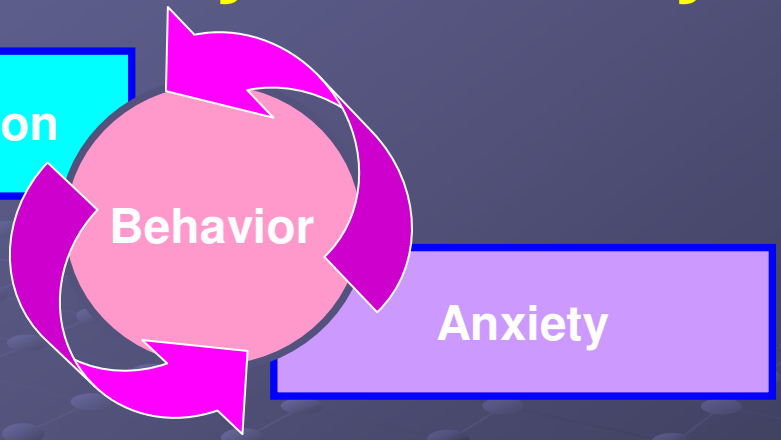


-/- mice



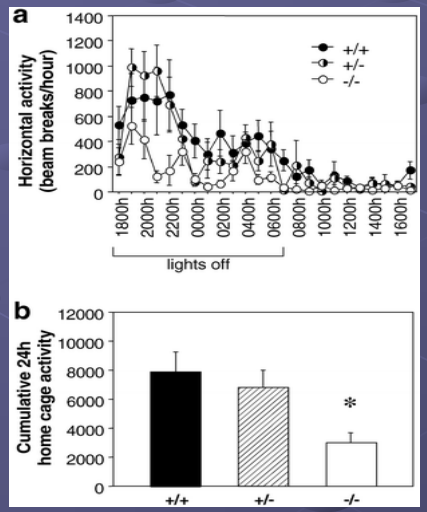
- Anxiety in multiple tests (Holmes et al., 2003, 2005)
- Inactivity (hypolocomotion) Kalueff et al., 2007

Domain interplay: inactivity vs. anxiety



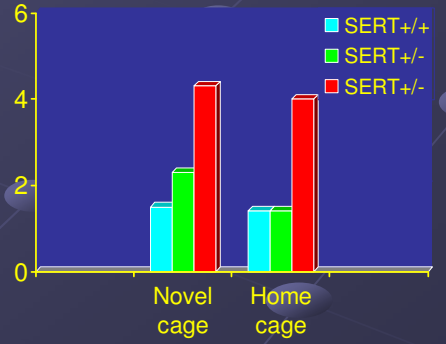
Q: Can some SERT-/- behaviors be due to hypolocomotion?

Marble burying test
- Anxiety
- Activity
- OCD-like behavior



Hypoactivity may dominate all other behavioral domains in SERT-/- mice

Number of non-buried marbles

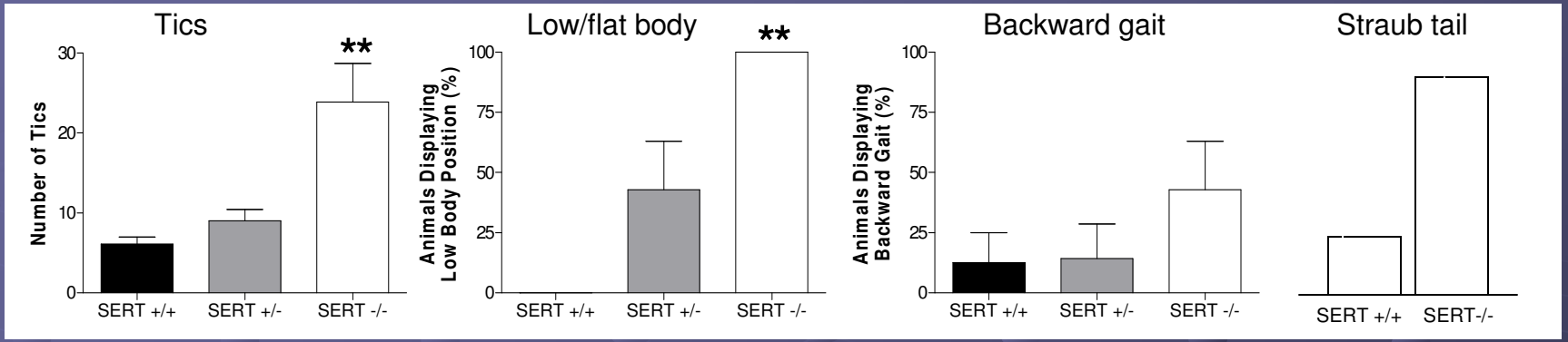


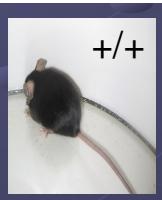
Holmes et al., 2002 Psychopharmacology

Kalueff et al., 2006, NeuroReport

Example: SERT-/- mice

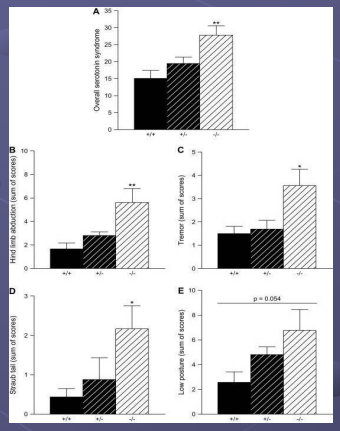
Serotonin syndrome behavior





Further pharmacological validation

MAO Inhibitor tranyl-cypromine



Fox et al., 2007, Neuropharmacology

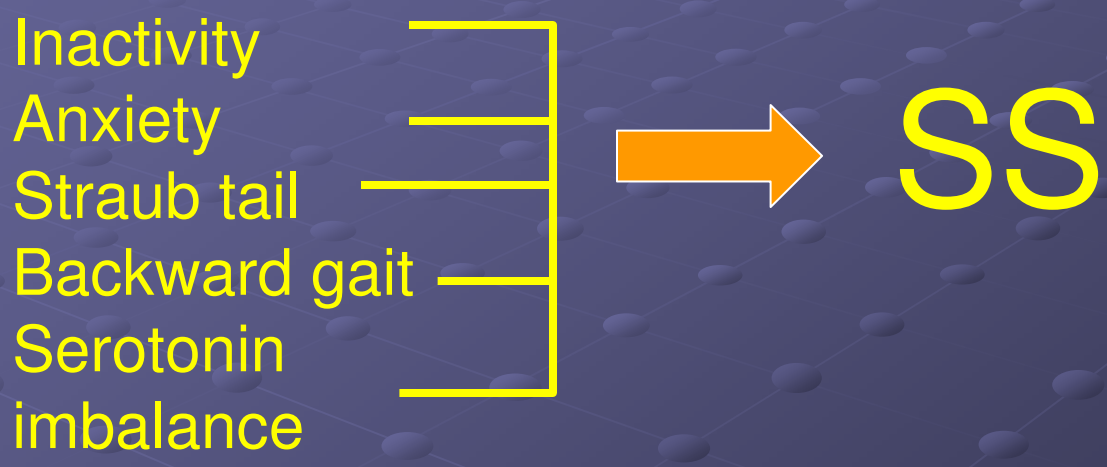
SS-like behaviors	Spontaneous SERT-/-	Drug-evoked SERT-/-
• Muscle rigidity	+	+
• Tremor	+	+
• Forepaw treading		+
• Head weaving		+
• Myoclonus (seizures)		
• Ticing, back muscle contraction	+	+
• Flat/low body posture	+	+
• Incoordination	+	+
• Hind limb abduction	+	+
• Backward gait		+
• Hyperthermia	+	+
• Straub tail	+	+

SERT-/- mice as a model of serotonin syndrome

Neurophenotype → Hypothesis → Model

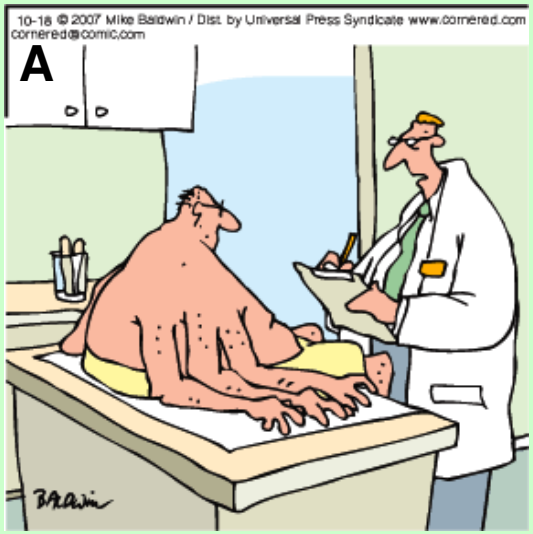
Kalueff et al., 2007, Genes Brain Behav

Interplay of domains



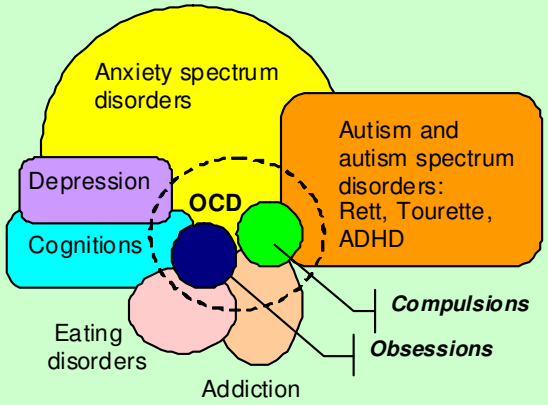
Complexity of psychiatric genetics and domain-interplay concept

Figure 1



Sounds like an obsessive-compulsive disorder. Normal people don't spend that much time washing their hands.

Spectrum nature of OCD and other neuro-psychiatric disorders



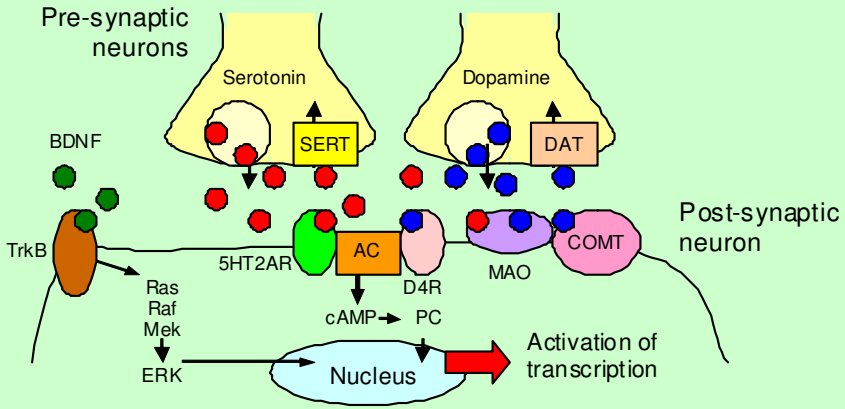
Animal candidate genes for OCD

SAPAP3
HoxB8
Dopamine transporter (DAT)

Human candidate genes for OCD

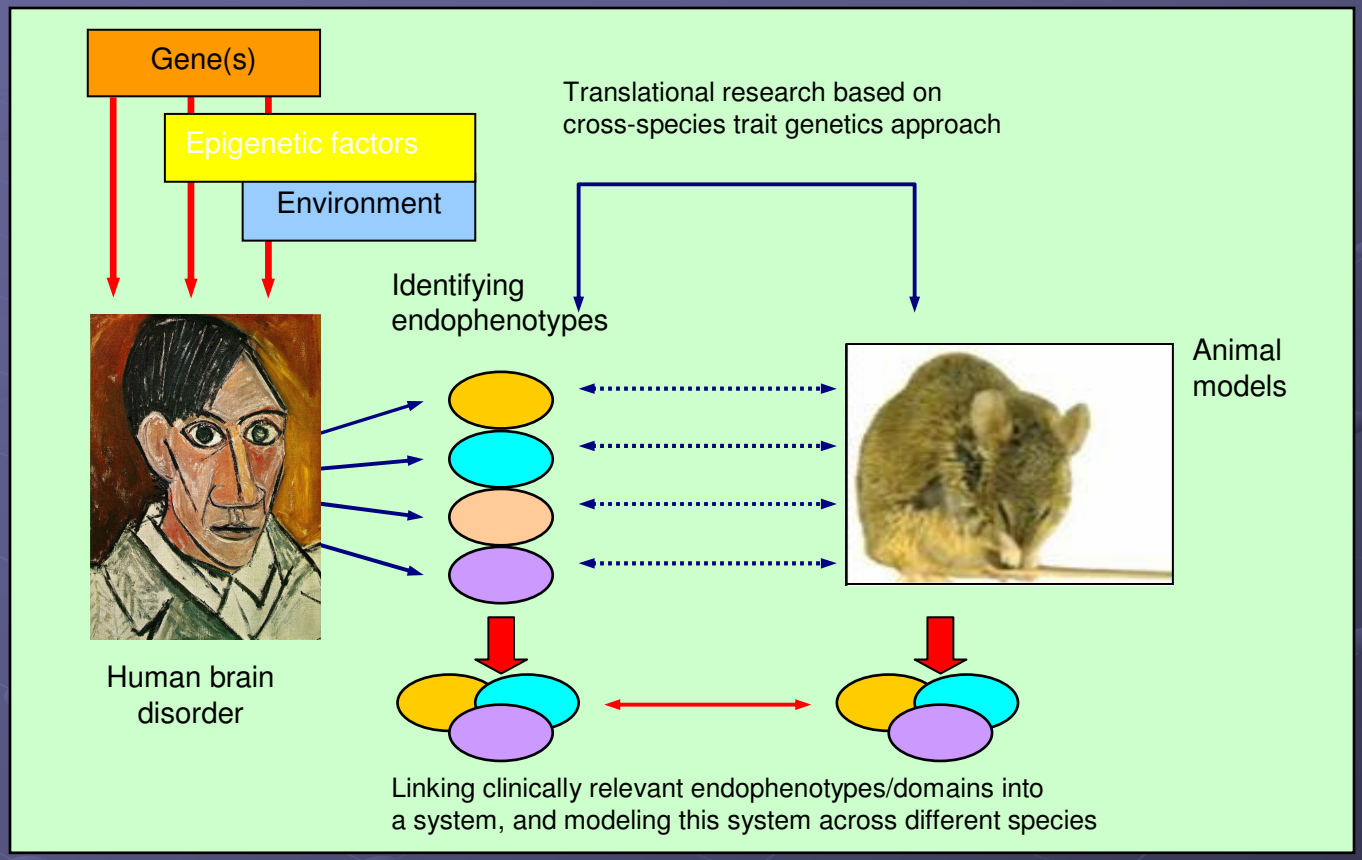
Glutamate transporter 1
Dopamine D4 receptor (D4R)
Serotonin transporter (SERT)
Serotonin 5HT2A receptor (5HT2AR)
Catechol-O-methyl transferase (COMT)
Monoamine oxidase (MAO) A
Brain derived neurotropic factor (BDNF)

B **Overlapping signaling pathways mediated by candidate genes for OCD**

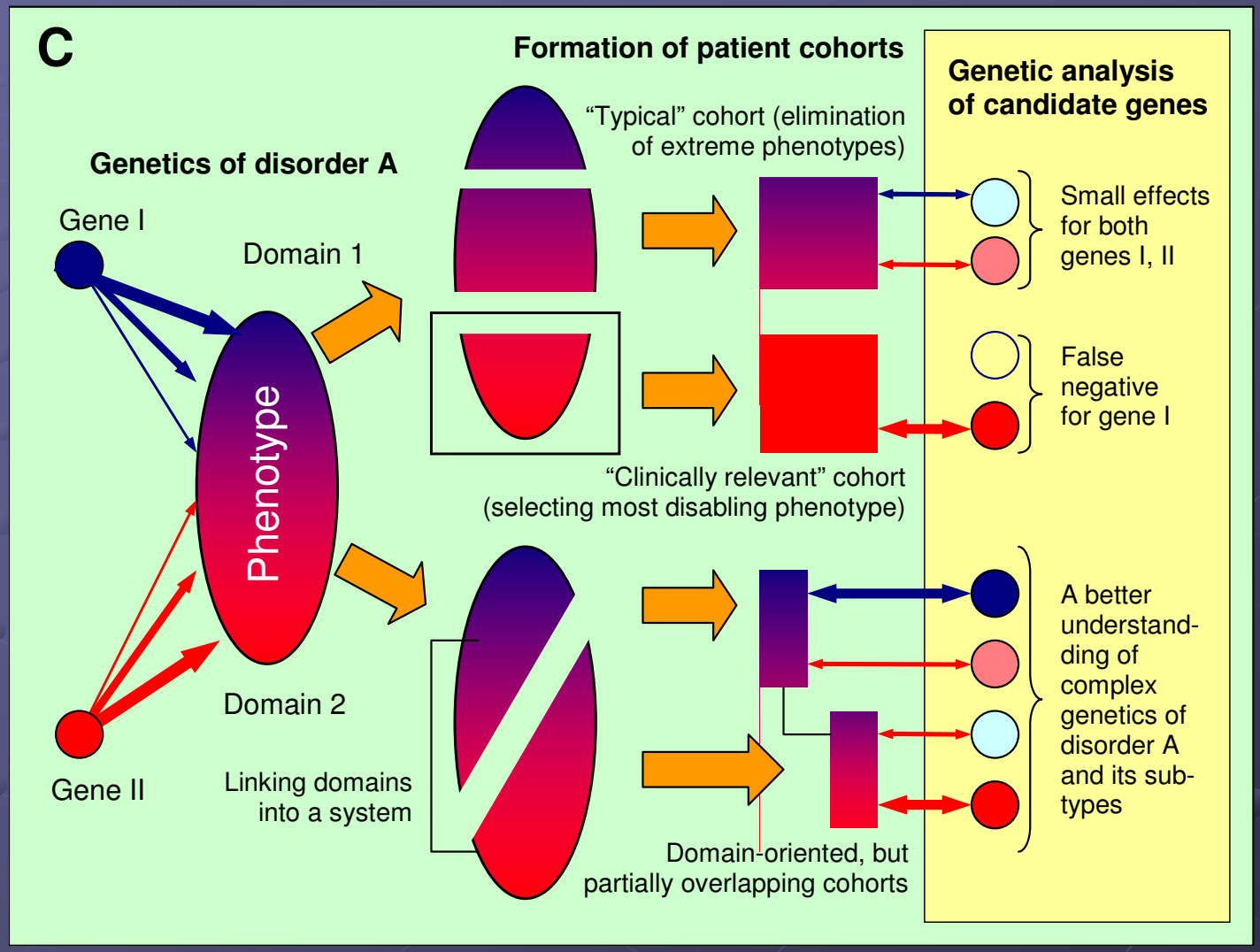


Psychiatric genetics of complex disorders: domains of OCD

Concepts of neurophenotyping research



Complex genetics of psychiatric domains



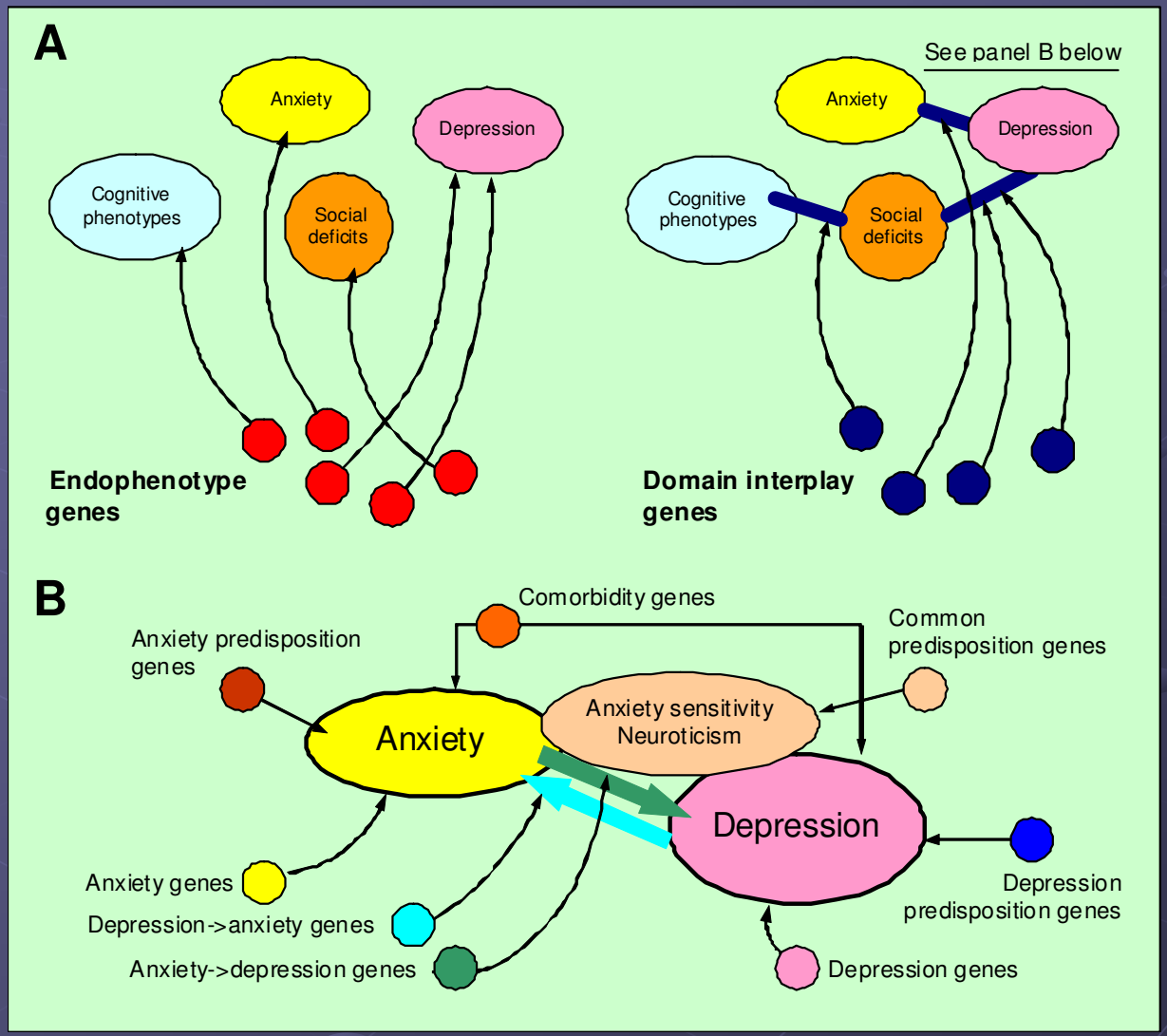
Summary

Domain interplay concept (vs. traditional domain-oriented approaches):

- Targets more domains per experiment (more high-throughput)
- Reduces animal experimentation
- Has more chances to “net” a new phenotype of interest
- Offers a fuller picture of complex phenotype
- Enables an integrative modeling of brain phenomena (continuum vs. “simple” disorders)
- More sophisticated psychiatric genetics:
  - “domain” genes
  - “comorbidity” genes
  - “domain interplay” genes

Kalueff et al., 2008, Behav Brain Res

Complex genetics of psychiatric domains




Cornered
by Mike Baldwin
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cornered@comic.com
"This is for my depression. Go get your own."