Hybrid Protocols in Neurobehavioral Research

1st ISBS Summer School

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May 9th -15th,2008

Challenges in behavioral neuroscience and psychopharmacology

Practical

- ↑ costs (space, animal, etc.)
- high variability of data
- animal welfare concerns

Conceptual

- incorrect dissection of phenotypes
- ↑ number of mutant animals/drug effects to phenotype
- ↑ complexity of phenotypes/drug effects

Traditional phenotyping approaches

Most neurophenotyping techniques are:

- focusing on a single domain/disorder
- time-consuming
- may be expensive

This highlights the need for ↑ through-outputful models

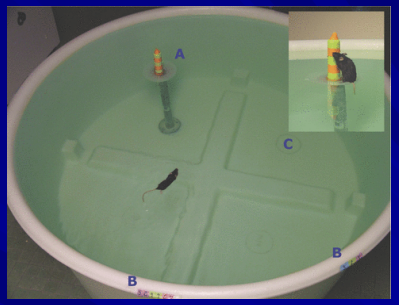
Solutions

- Test batteries
- Consider previous experience of model in each stage of tests

Test 1 → **Test 2** → **Test 3** → **Test 4**

This promotes efficiency and high-throughput

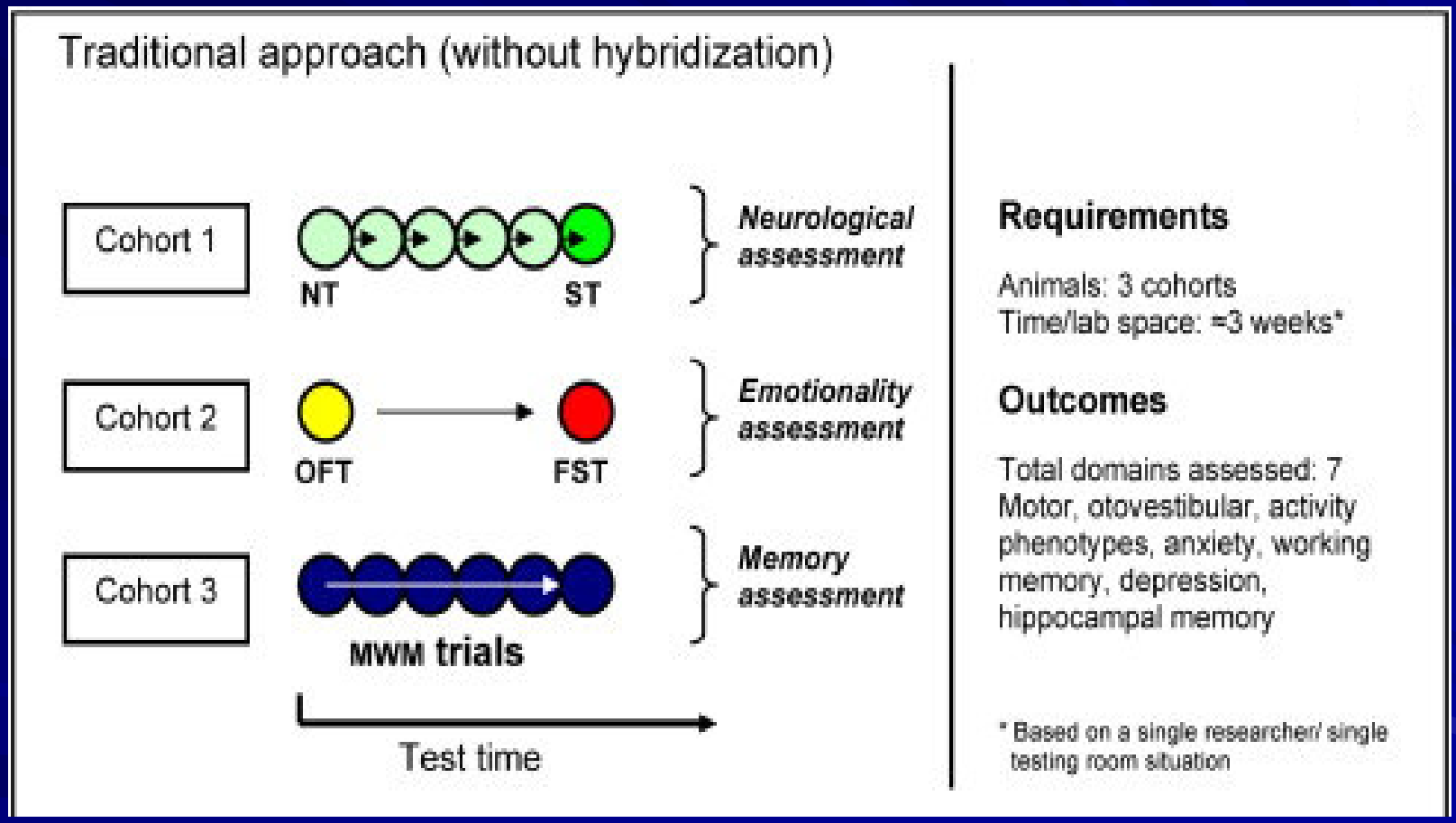
Forced Swim Test



Morris Water Maze

Elevated Plus Maze

Traditional phenotyping



Kalueff et al., 2008. Prog NeuroPsychopharmacol Biol Psychiatry

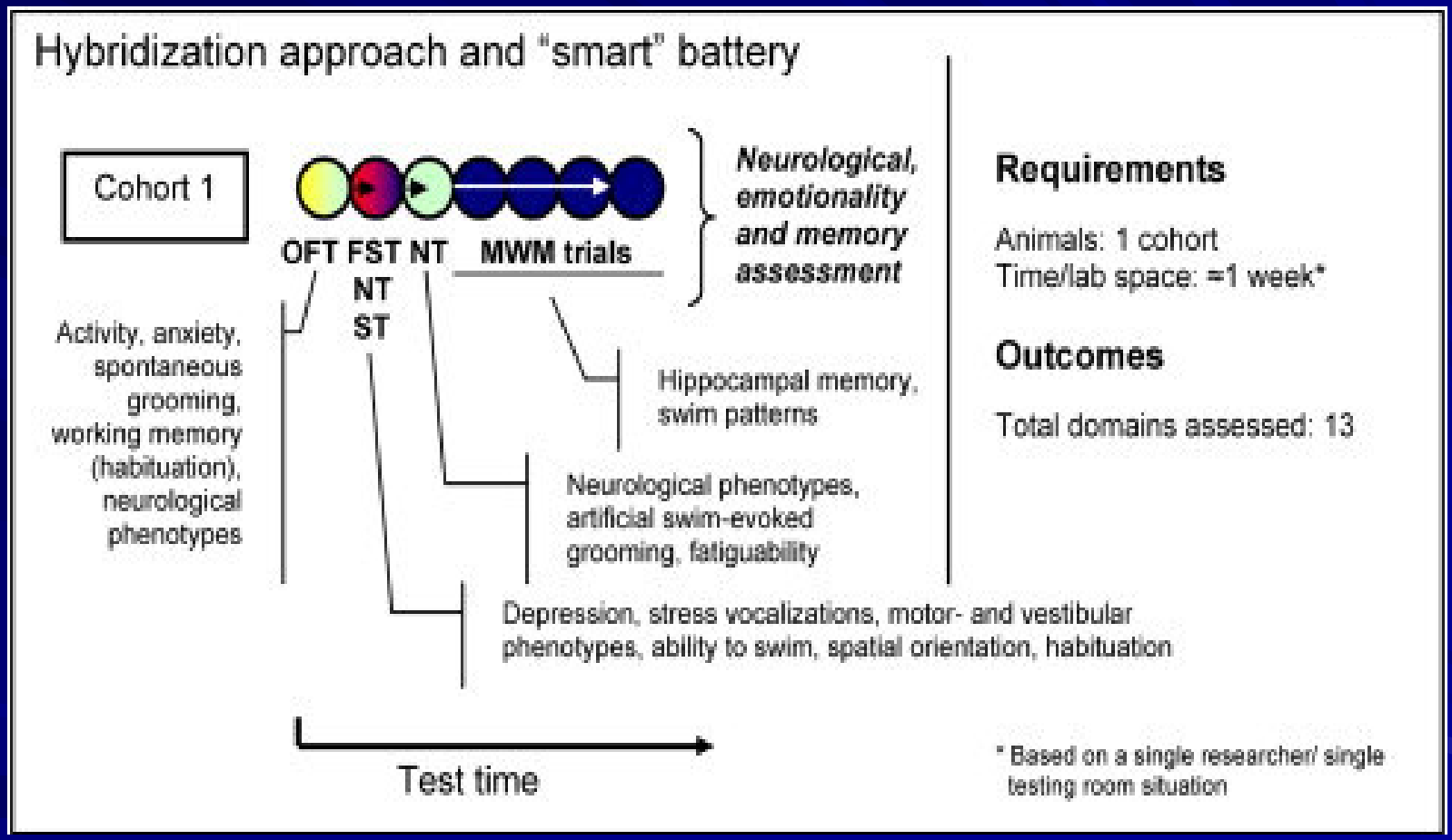
What are hybrid models?

Hybridizing concept:

- Protocols that assess multiple domains in parallel
- "Smart batteries" - protocols that logistically combine experimental paradigms to maximize the number of tested phenotypes per experimental manipulation.

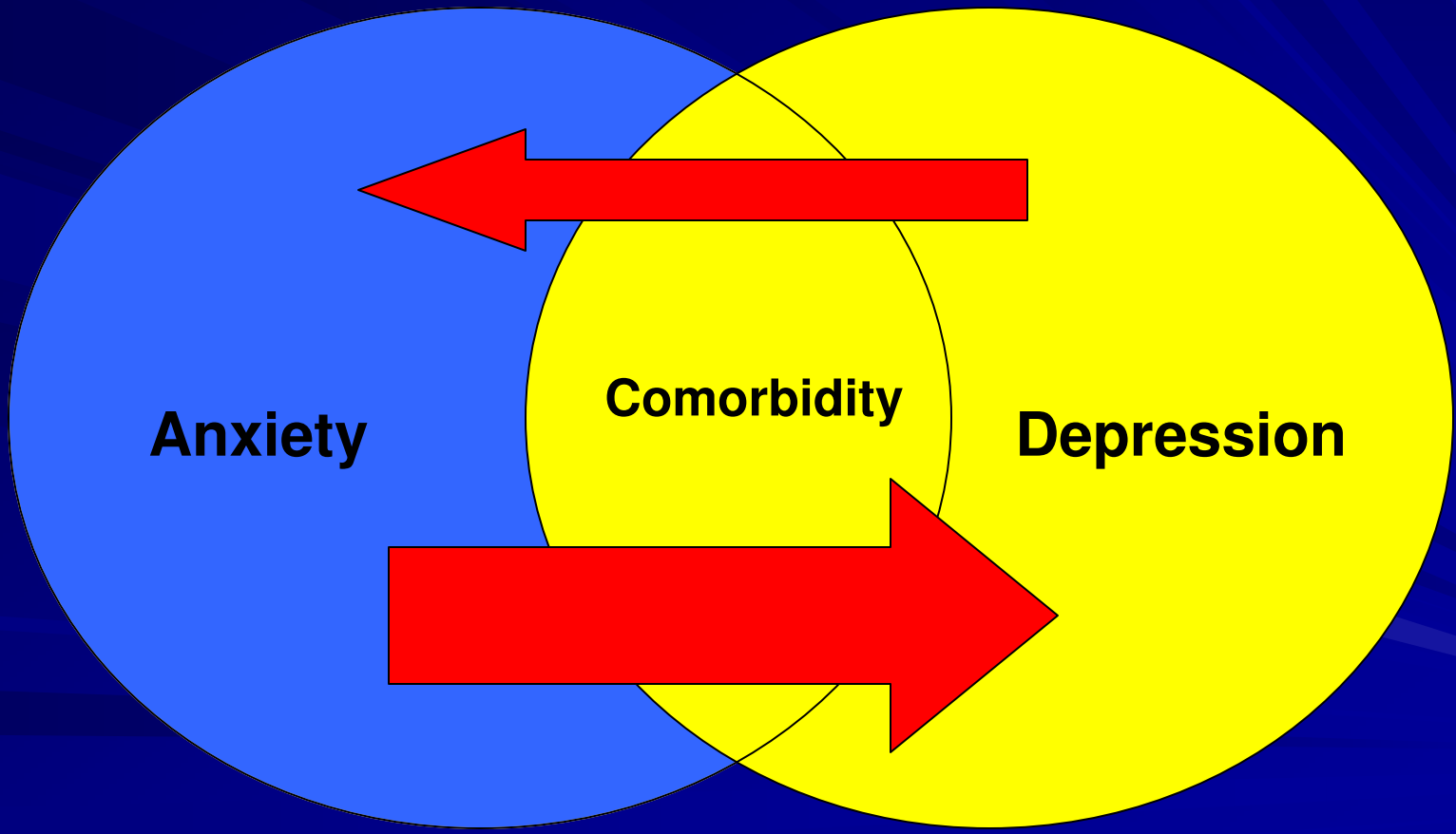
Kalueff et al., 2008. Prog NeuroPsychopharmacol Biol Psychiatry

“Hybrid” approach



Kalueff et al., 2008. Prog NeuroPsychopharmacol Biol Psychiatry

Comorbidity of anxiety and depression



Example 1: Hybridization approach - chronic social defeat paradigm in mice

- Mimics anxiety and depression in males
- Requires 20 days of repetitive social defeat

C57 mice
Chronic social defeat

Kudryavtseva et al. 1990-2007

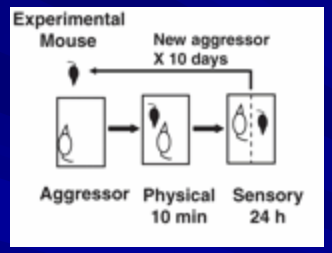
Social defeat model

Social stress-based model (Kudryavtseva, 19

- social winners or losers in male mice
- daily social confrontations
- daily non-contact exposures to winners
- anxiety (10 days) and depression (20 days)
- sensitivity to antidepressants or anxiolytic drugs

Pathophysiology

- ↑ DA and ↓ 5HT (winners), ↑opioid system (losers)
- ↑ immune deficiency
- ↑ susceptibility to transplanted tumor growth



Bridging behavior and genetics

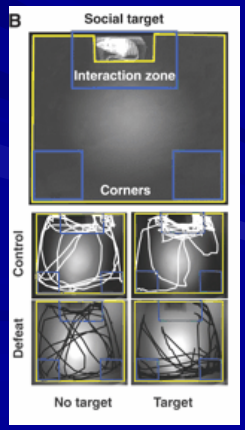
Aggressive mice:

↓ mRNA of catechol-O-methyltransferase

↑ mRNA of DAT and tyrosine hydroxylase

Submissive mice:

Repeated defeats ↑ mRNA of SERT, MAOA



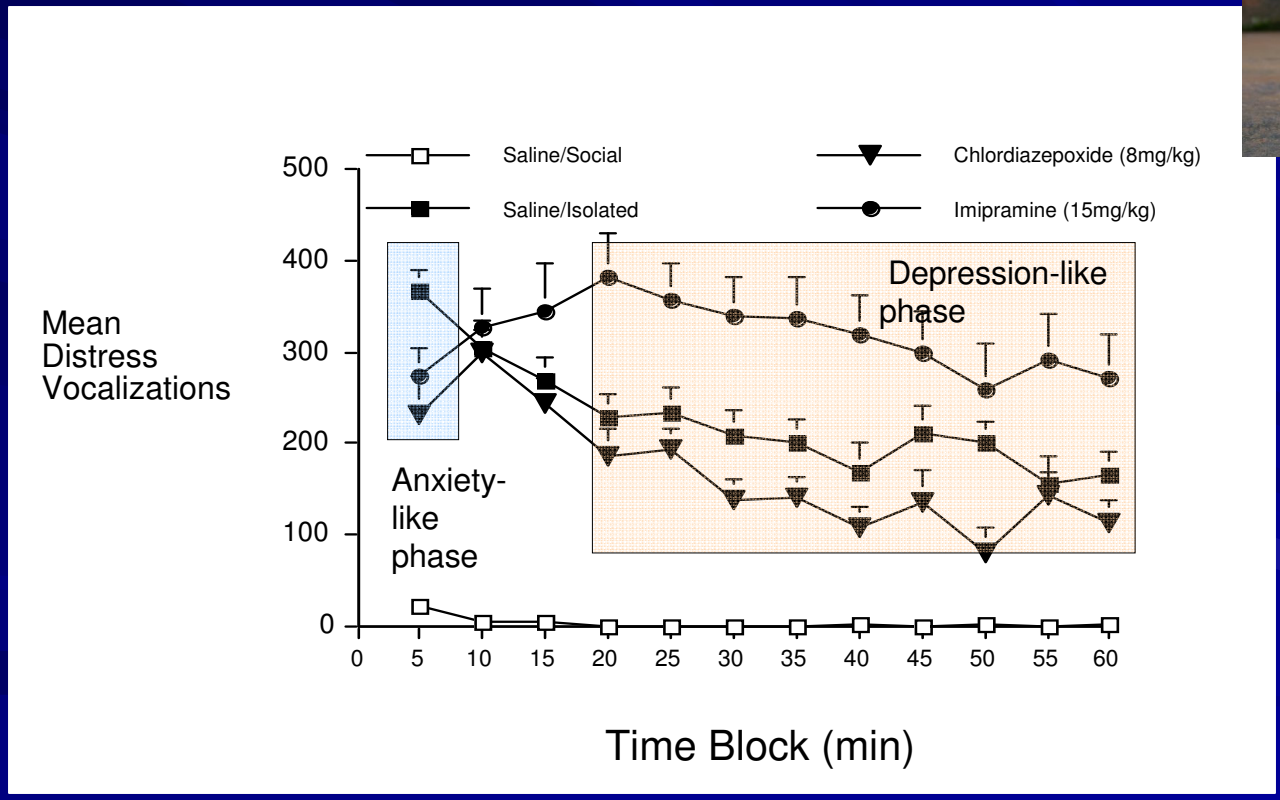
Complex mouse behavior

- *Berton et al. Science, 2006*
- *Kalueff et al. Science, 2006*

Applications to humans

Example 2: Hybridization approach - 2 domains tested in 60 min in chicks

- Socially-raised chicks were separated from peers
- Their "distress vocalizations were recorded

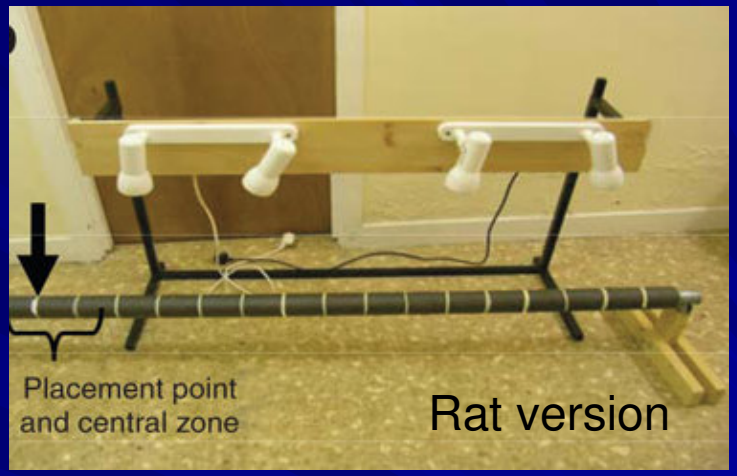


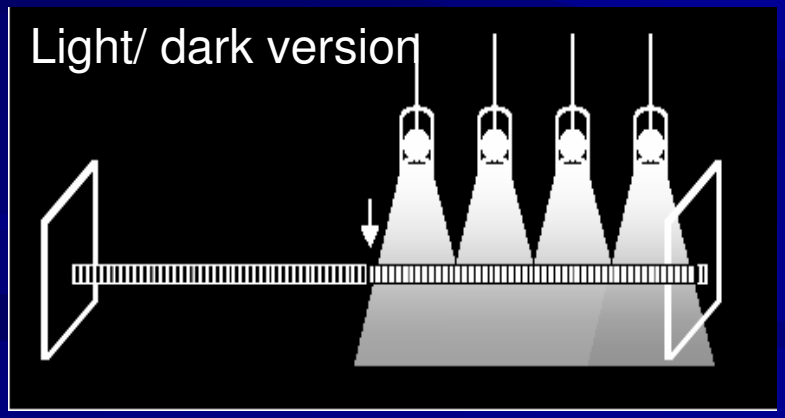
Sufka et al., 2006 Behav Pharmacol

Advantages of Hybrid Models

- Easy implementation
- Can assess more domains/disorders per experiment
- Reduction of animal numbers/suffering
- Target several behavioral endpoints
- High-throughput
- Less expensive (than a battery of single-domain models)
- Can mimic more complex clinically-relevant phenomena (e.g. comorbidity)
- Can “net” complex phenotypes

Example 3: The Suok test of anxiety and balancing



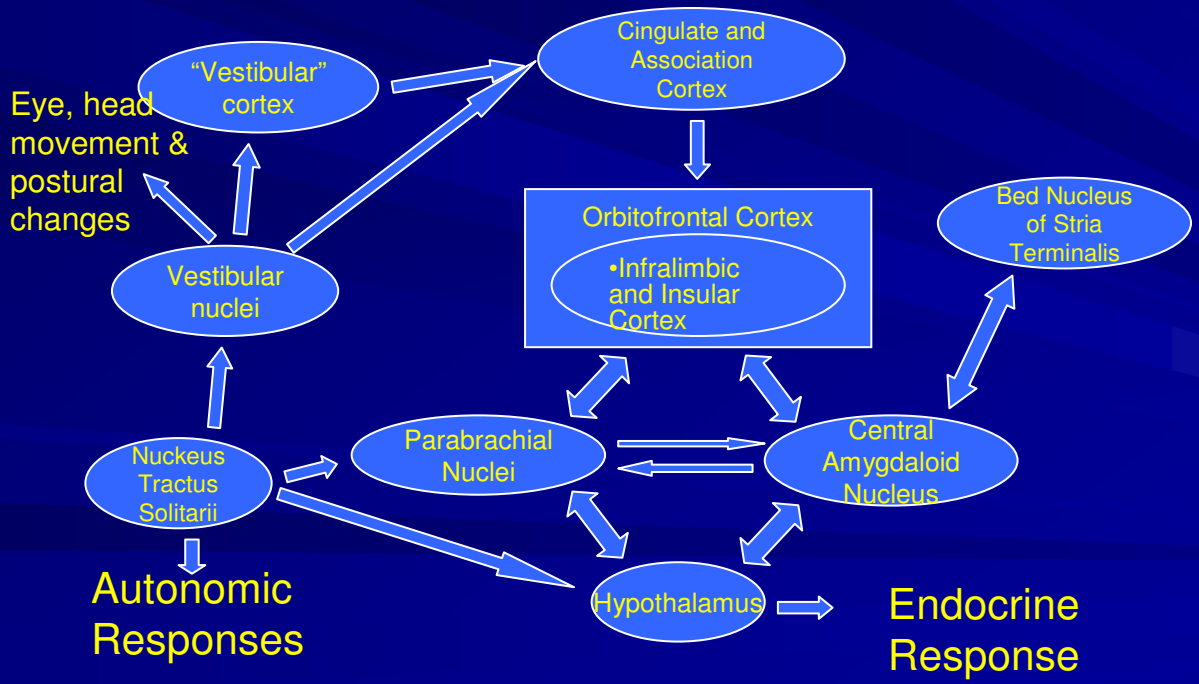


Kalueff et al., 2008. Nature Protocols

Neurobiological Rationale: Domains tested

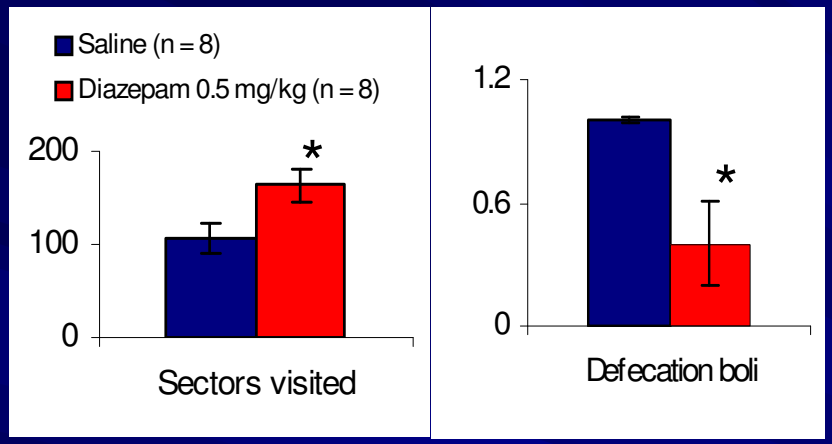
- Anxiety
- vestibular disorders
- coordination
- anxiety-vestibular interplay
- balancing
- motor control

Common neural circuits for anxiety and balancing

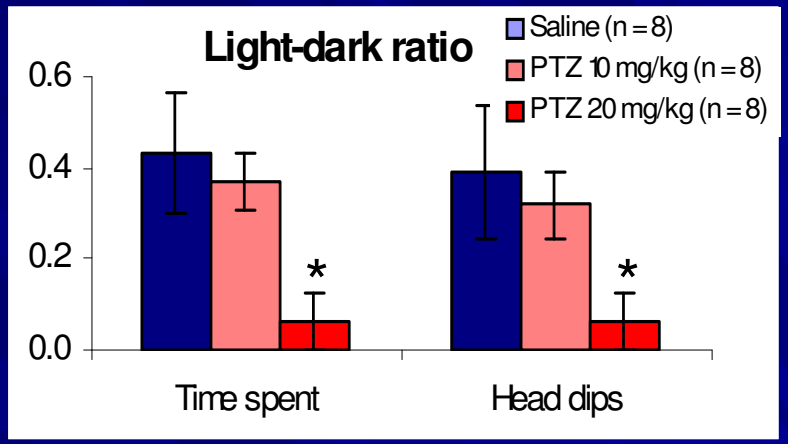


Suok Test pharmacology

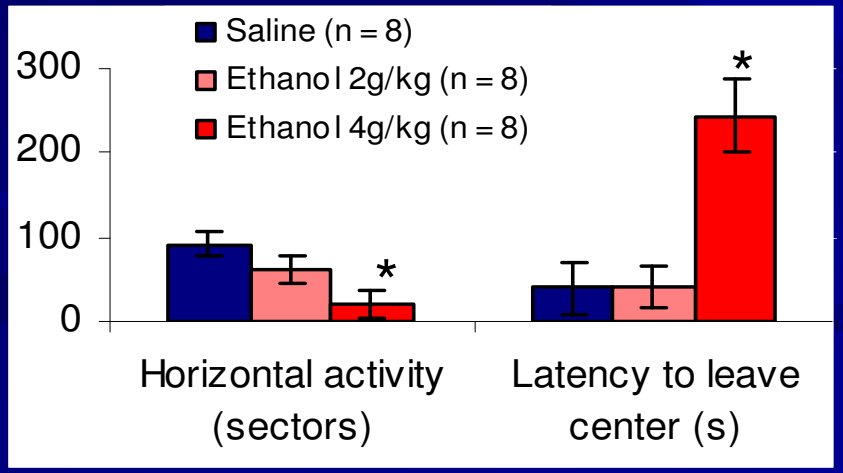
Regular BALB/c mice



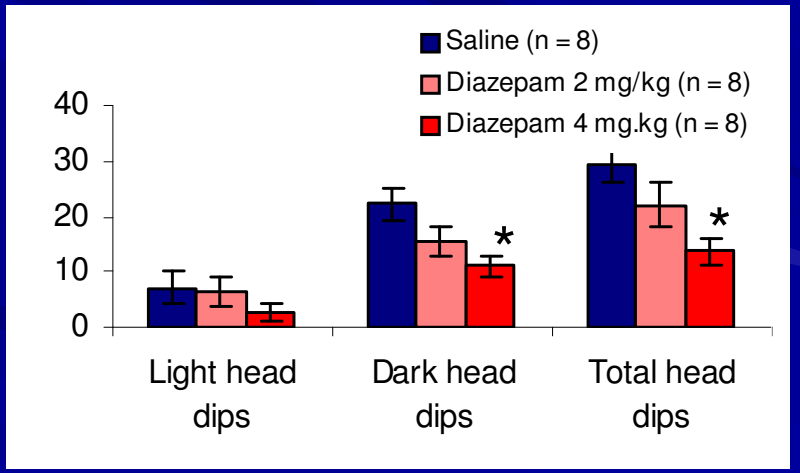
Light/dark BALB/c mice



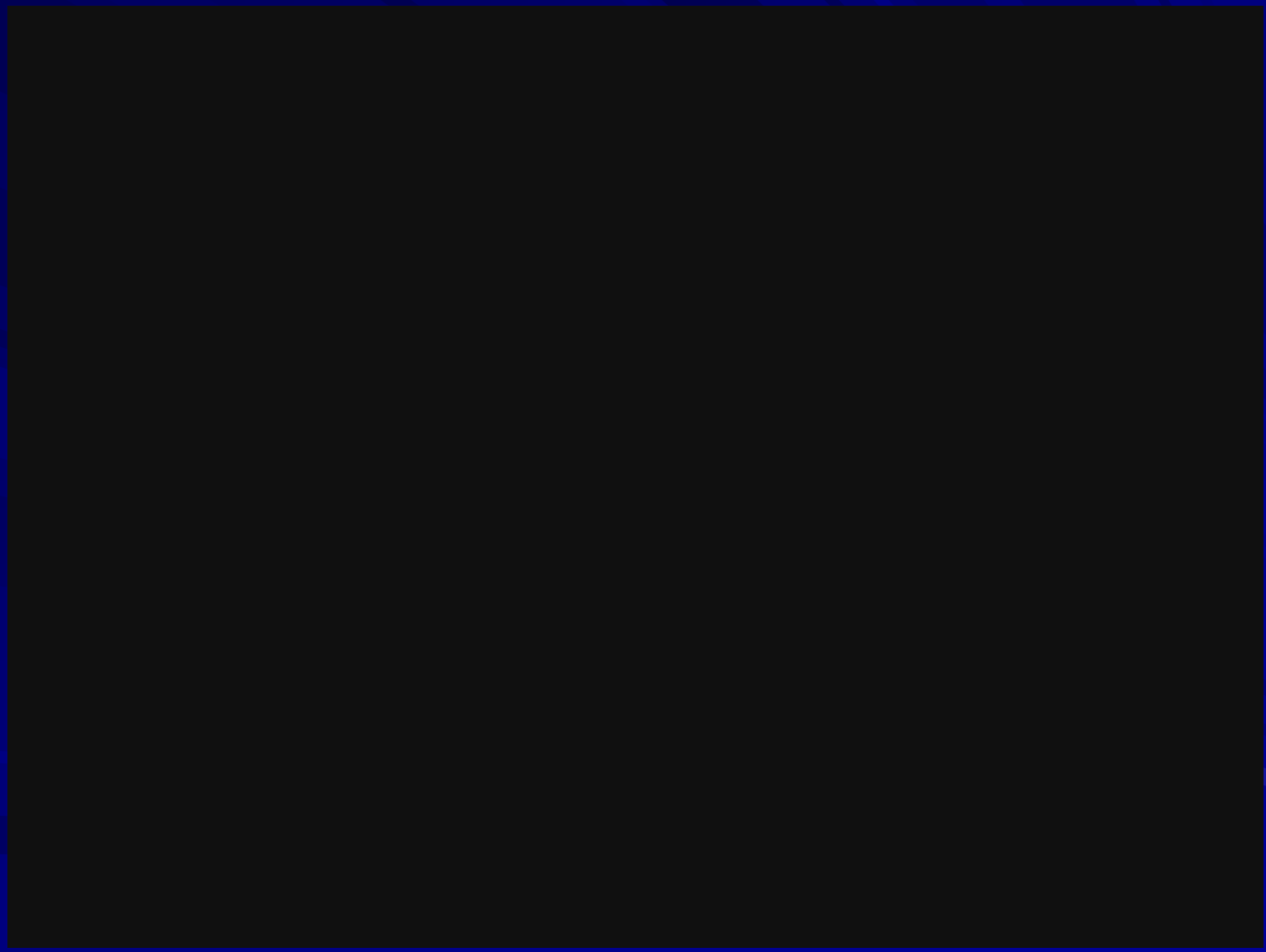
129S1 mice



129S1 mice



Animal behavioral performance on the regular Suok test (CD-1 mice)



Other “hybrid” protocols

Stress hyperthermia	Baseline temperature assay, anxiety
Grooming sequencing	Anxiety, OCD-like phenotypes, Tourette’s syndrome-like phenotype
Wheel running	Motor activity, circadian rhythms, social stress, anxiety
Chronic stress paradigm	Anhedonic depression, anxiety, motor activity

Other “hybrid” protocols

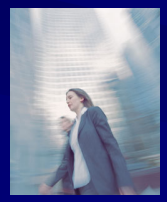
Compulsive drug intake	Reward, drug abuse phenotype, OCD-like phenotypes
Tail suspension test	Depression (immobility), vestibular abnormalities (spinning), specific neurological phenotypes.
Marble burying	Anxiety, motor activity, OCD-like phenotype
Social interaction	Anxiety, activity, aggression, autism-like phenotypes
Y- or T-maze	Spontaneous alternation, spatial memory, anxiety, OCD-like phenotypes

Traditional concepts in biological psychiatry

Genes

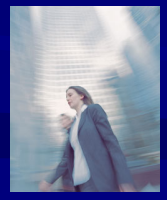
Genes

Endophenotype



Environment

Genes



Environment

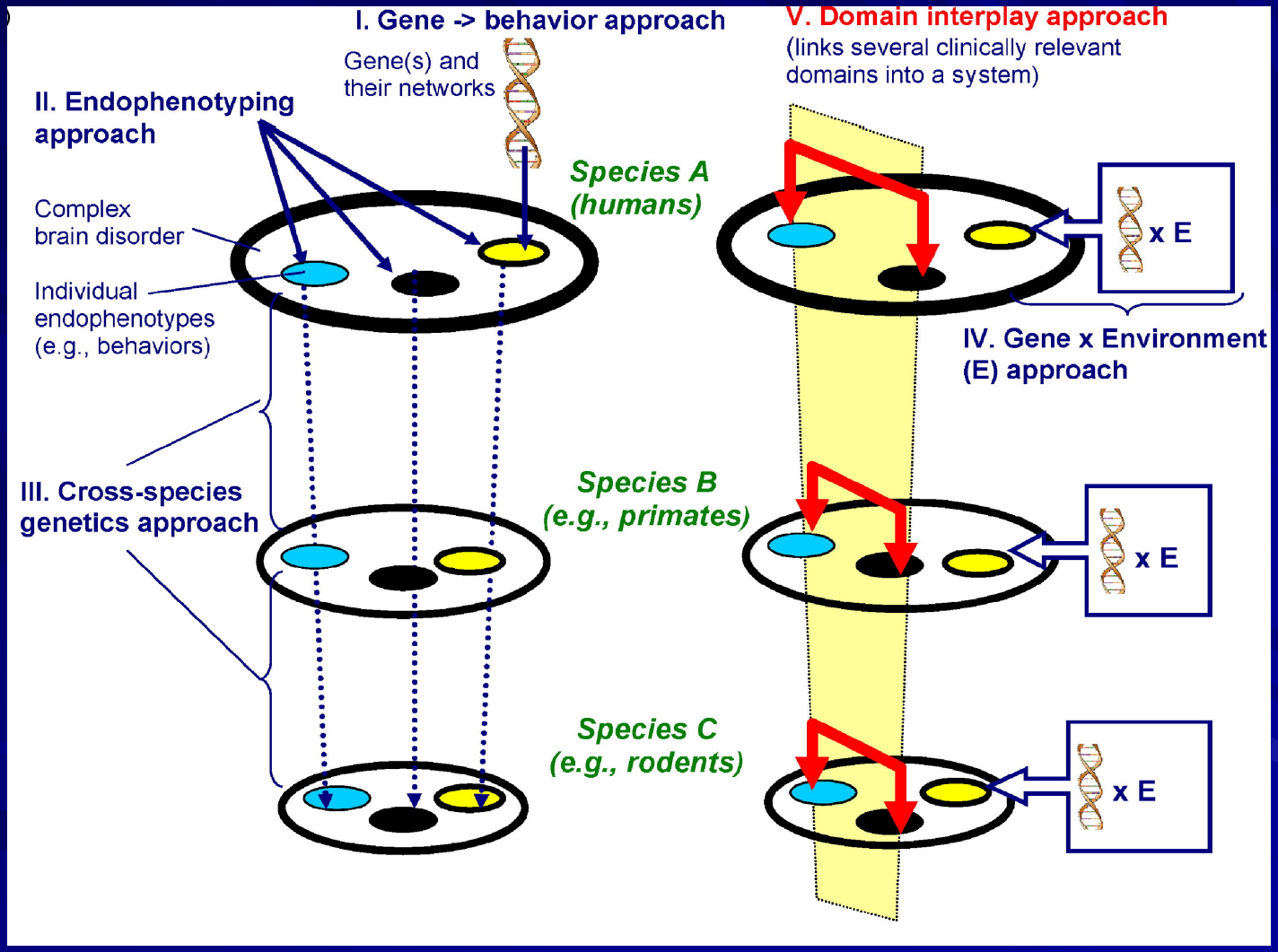
Genes

Neural substrate reactivity

Disorder

Caspi et al., 2006

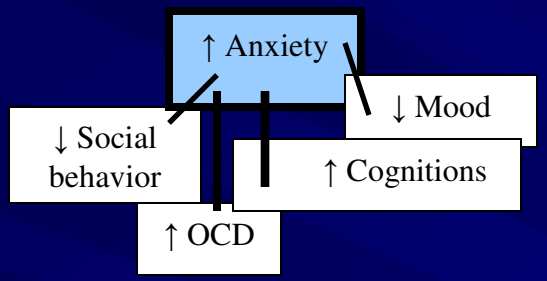
Domain interplay concept



Kalueff et al., 2008. Behav Brain Res

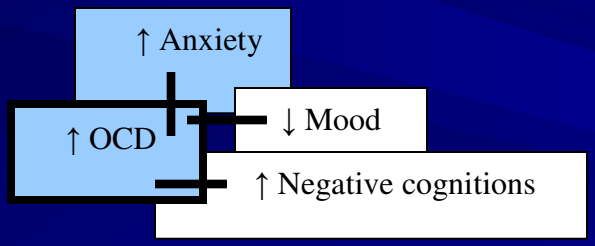
Domain interplay concept

Generalized anxiety

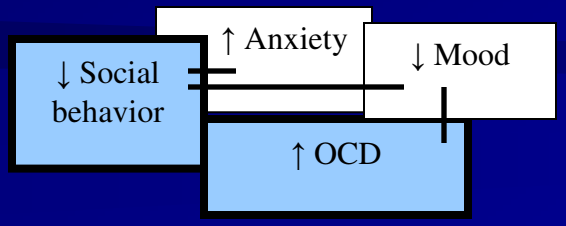


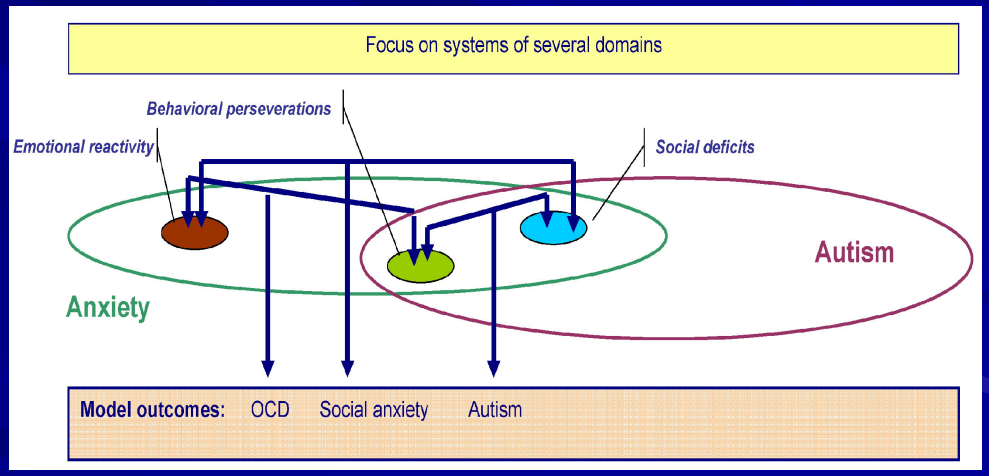
- parallel overlaps seen in clinical data
- better dissect comorbid disorders
- improve construct validity of models
- elucidate pathogenesis

Obsessive-compulsive disorder



Autism





Kalueff et al., 2008. Behav Brain Res

Integrating hybrid and domain concepts

The hybrid concept meshes with domain interplay

Hybrid modeling

Domain-oriented modeling

Both concepts:

- Targets several (at least two) domains

Conclusions

- The use of hybrid models is an important strategy in behavioral neuroscience research
- The hybridizing approach, in combination with the domain interplay concept, may accelerate the discovery of new pathogenetic mechanisms of brain disorders, and their integrative modeling
- This approach, based on a wider use of hybrid multi-domain models, may help discover new genes and drugs to treat brain disorders – which is the ultimate goal of our research

Finally she began responding to treatment.