Experimental animal models for the simulation of psychiatric diseases

Experimental animal models

- Animal models attempt to reproduce behavioral and physiological features that are indicative of the emotional state, the etiology of the disease and the effect of therapeutic intervention

- In a ideal and perfect model, etiology, symptom profiles and treatment responses would be identical to those seen in the human diseases

Animal models of anxiety

- Initially based on the effects of the only effective anxiolytics drugs, benzodiazepines, try to simulate the cardinal symptoms of anxiety but not of depression

- Pathological anxiety is not an excess of normal anxiety since different pathological forms seem to have different neurobiological basis and are differentially sensitive to pharmacological treatment

- At present, model of anxiety are distinct in models for normal anxiety (unconditioned and conditioned responses) and for pathological anxiety

Model based on unconditioned responses
Model based on exploration: Elevated plus maze Zero maze Open field Hole board Light/dark test
Model based on social behavior: Social interaction test Social competition
Stress- induced modification of behavioral and/ or physiological responses: Consummatory behavior Thermic response Corticosterone response
Miscellaneous: Marble- burying Anxiety test battery

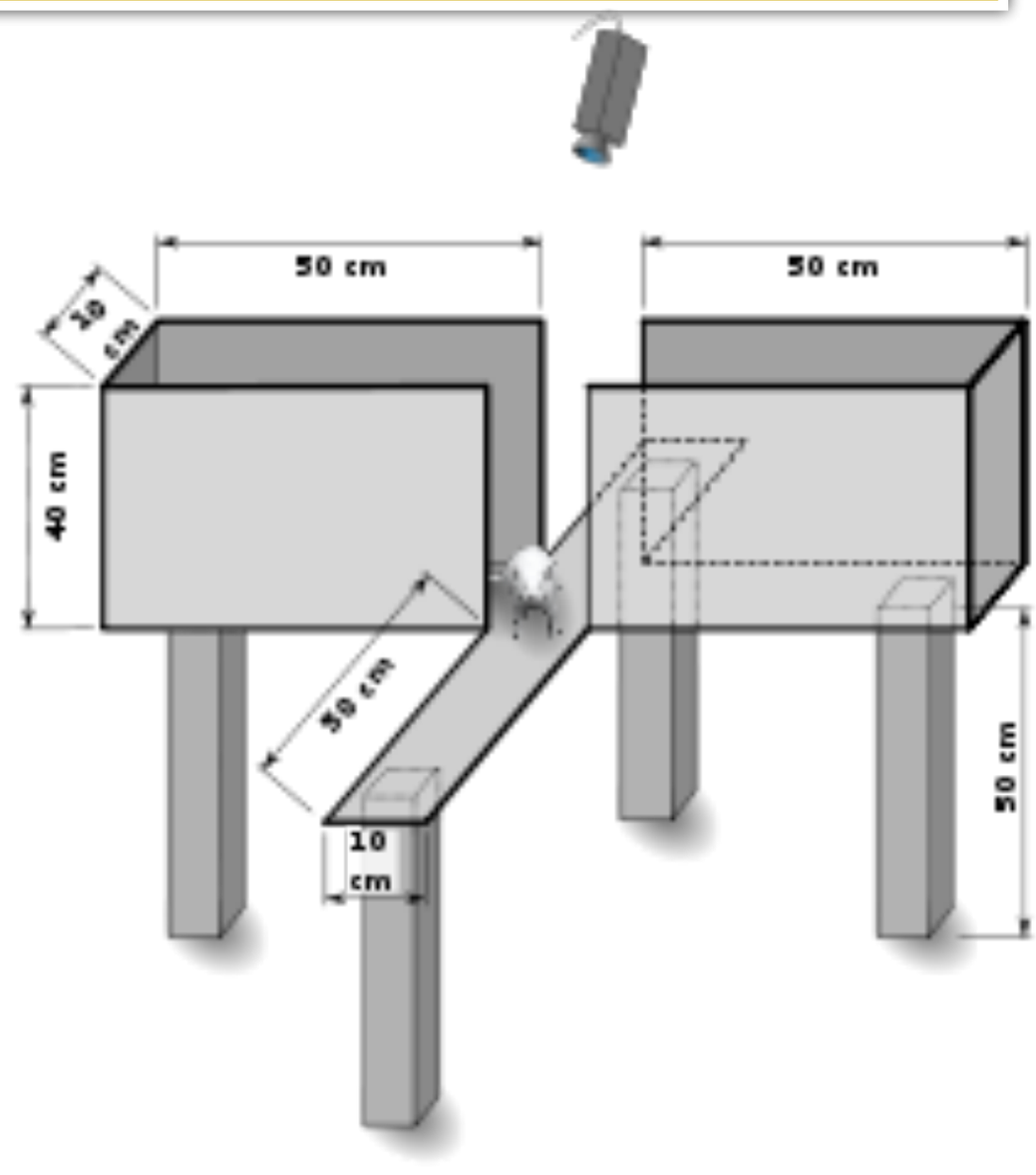
Model based on conditioned responses

Conflict tests:
Geller-Seifter
Pigeon and monkeys conflict
Vogel

Miscellaneous:
Fear potentiated startle reflex
Shock- probe burying test
Conditioned taste aversion
Active/ passive avoidance
Conditioned emotional response

Animal model of normal anxiety
Based on unconditioned responses

Elevated plus maze



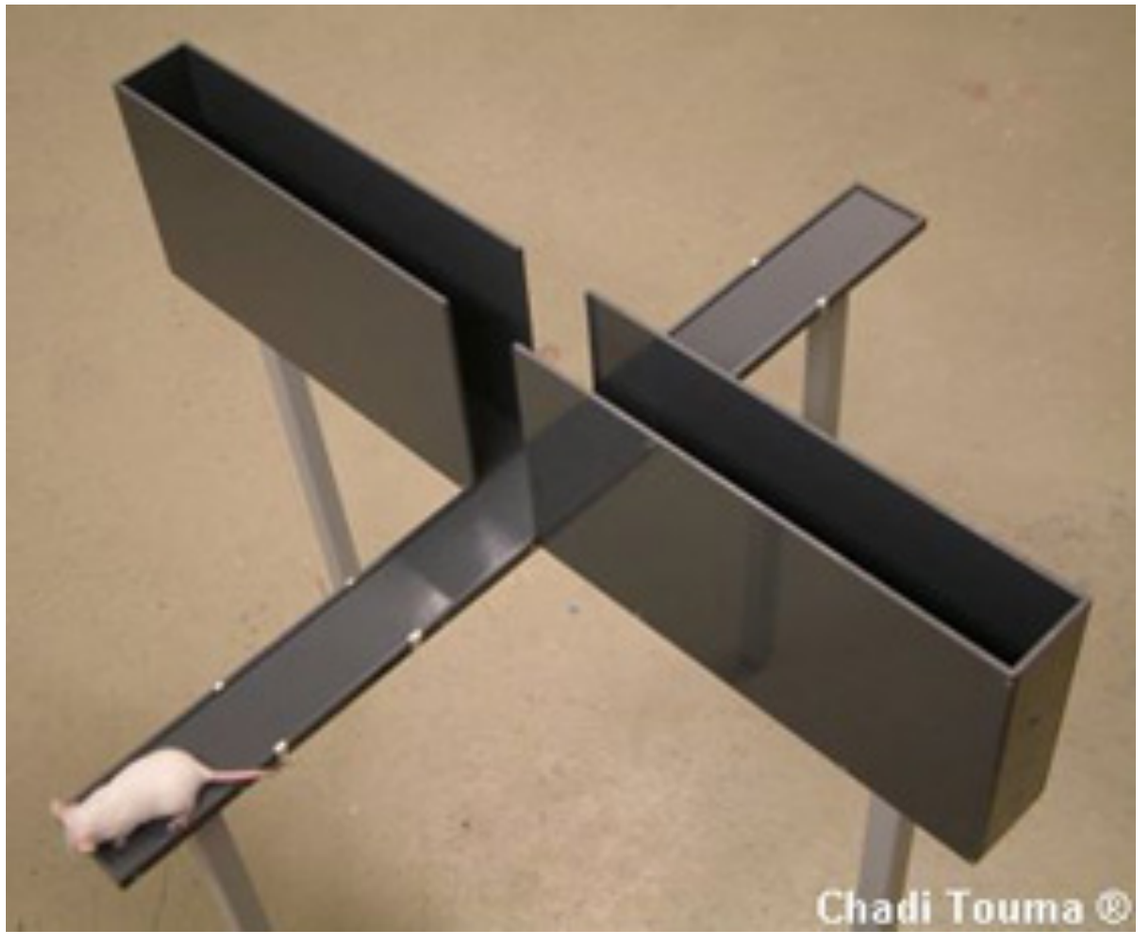
- One of the most popular model that relies on the natural behavior of the animals
- Permits quick screening of potentially useful drugs without training

Animal model of normal anxiety
Based on unconditioned responses

- The behavior pattern may be influenced by species and strain, housing conditions, day time, intensity of light, etc

- Introduction of ethological behaviors (dippings, rearings) in addition to spatial temporal measures increase sensitivity

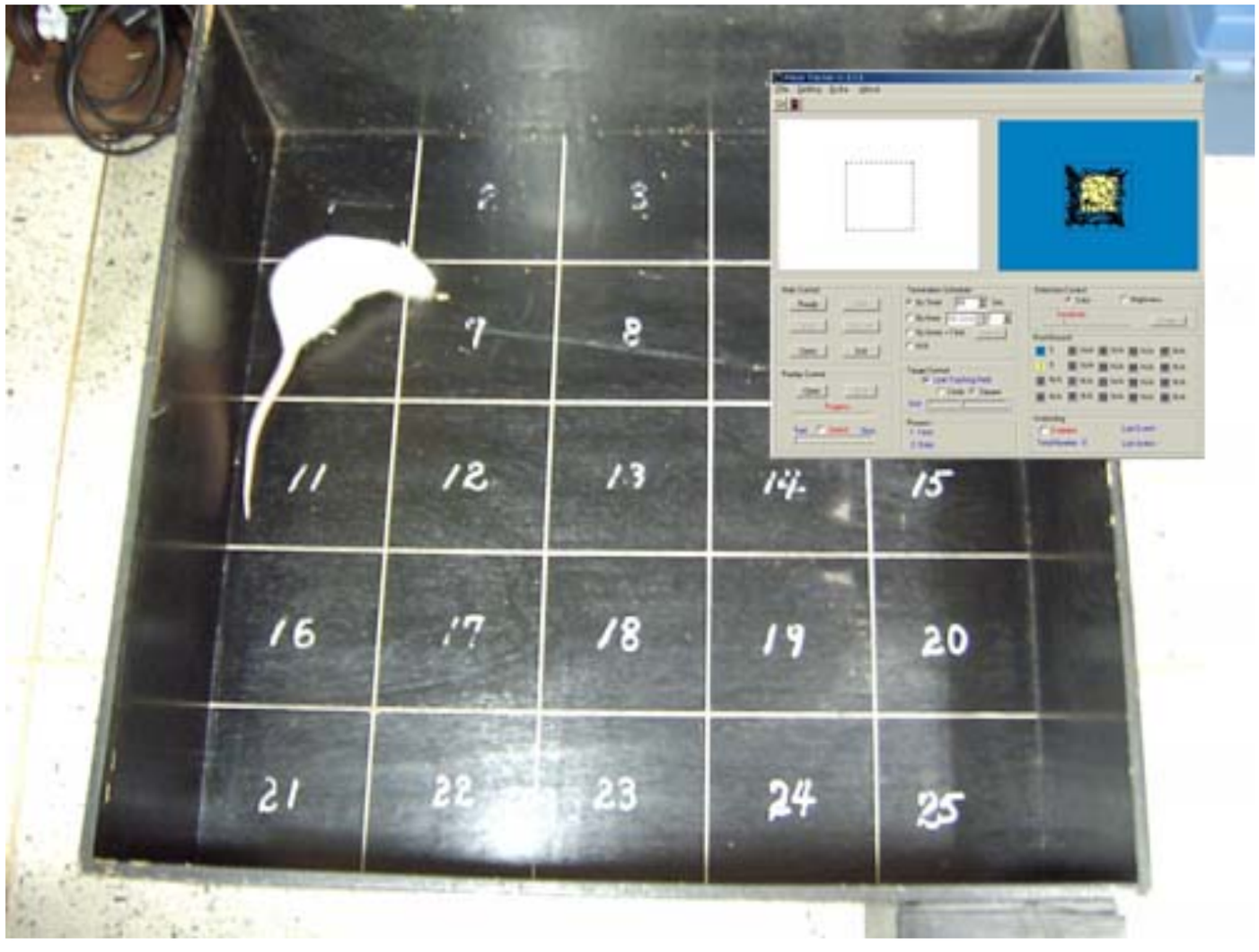
Elevated plus maze



Animal model of normal anxiety
Based on unconditioned responses

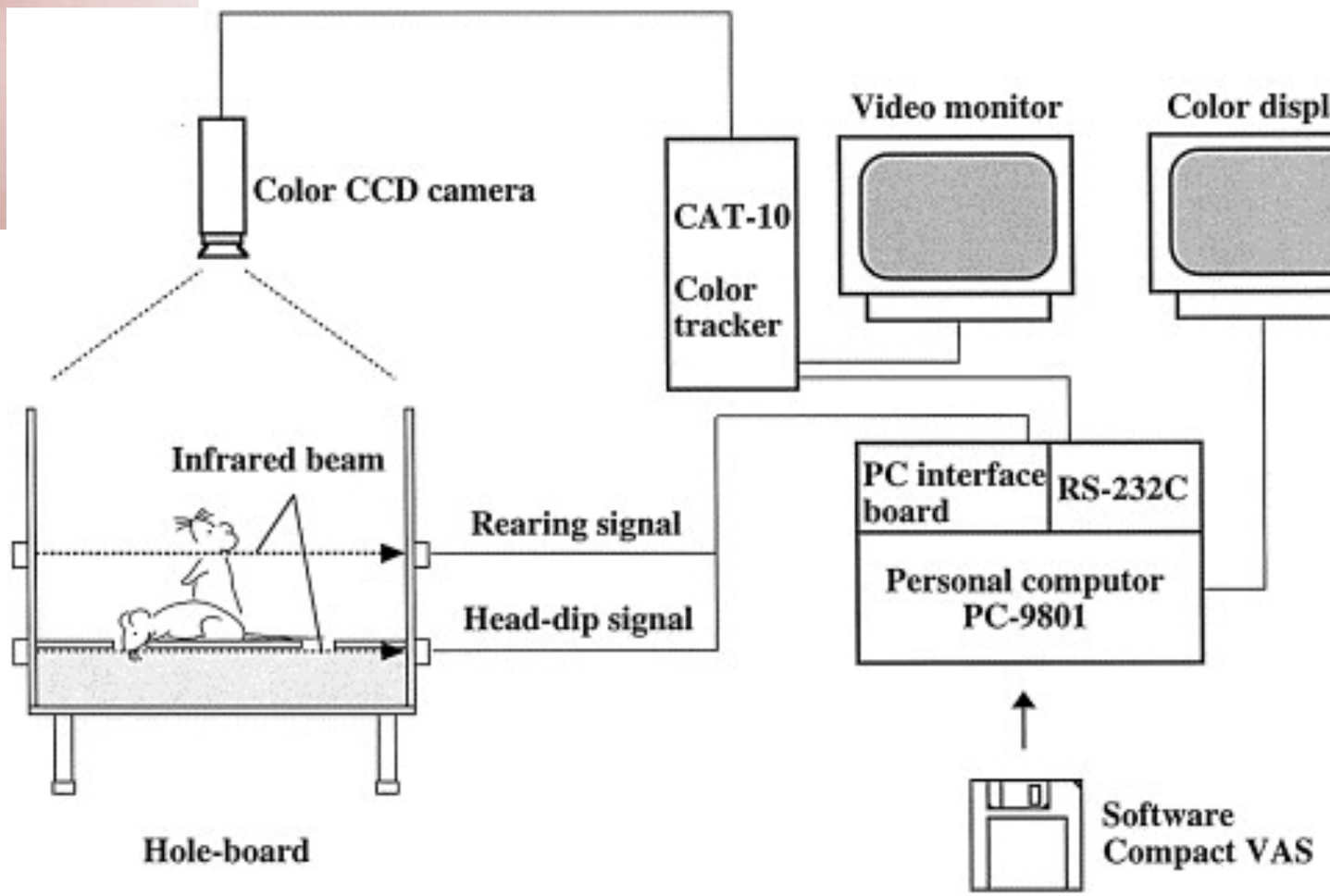
Open field test

- Measures both locomotor and exploratory behavior, autonomic activity (defecation, urination)
- Like elevated plus maze, sensitive to a variety of internal and external factors



Animal model of normal anxiety
Based on unconditioned responses

Hole board

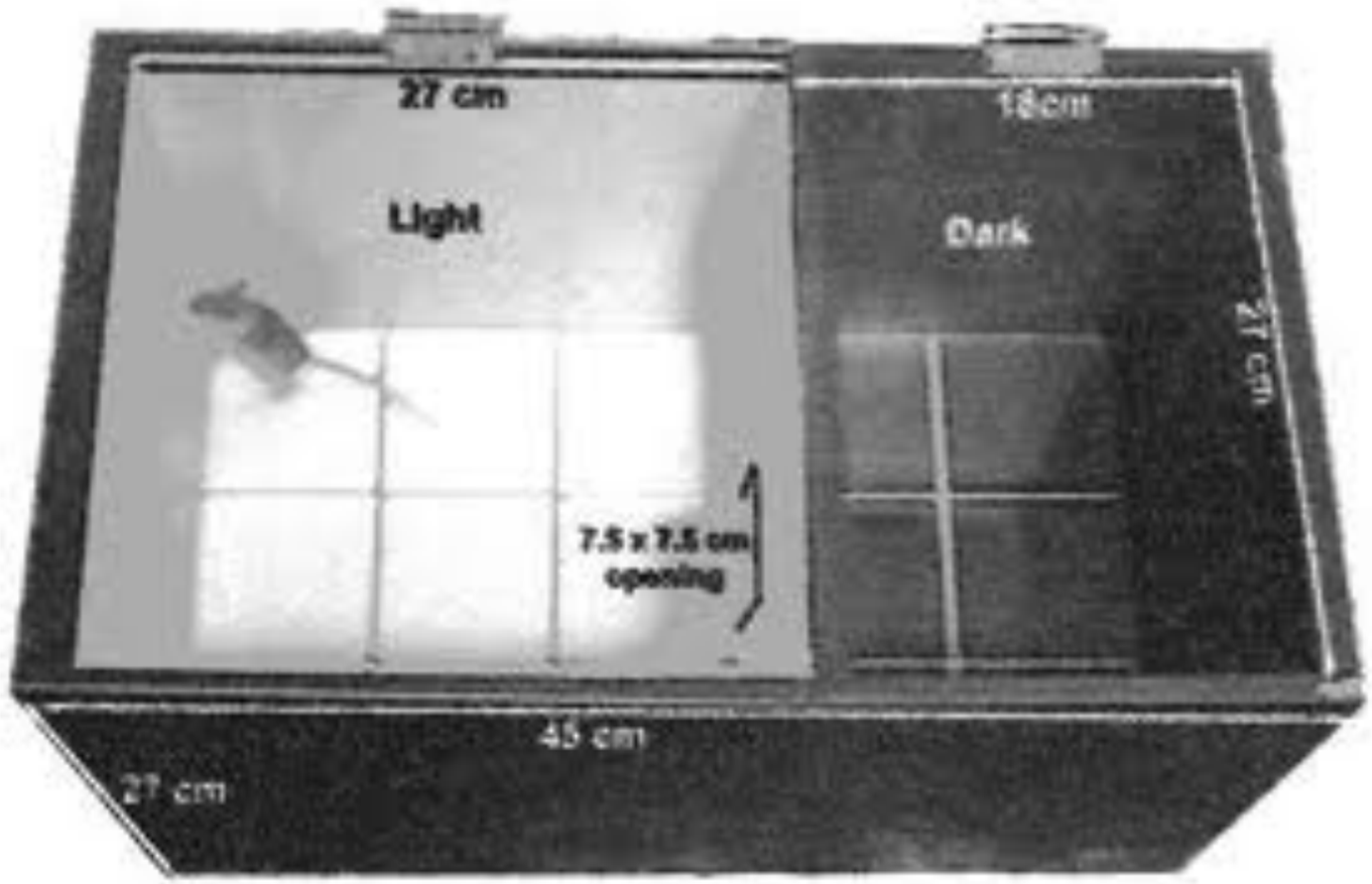


- Measures mostly the exploratory behavior

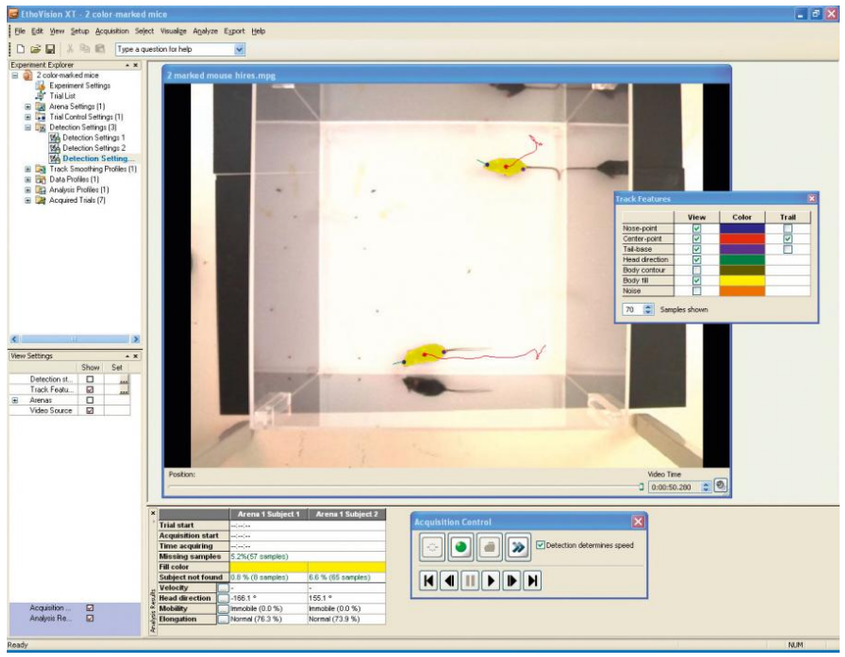
Animal model of normal anxiety
Based on unconditioned responses

- Measures exploratory behavior in contrast to the tendency of rodents to avoid bright areas

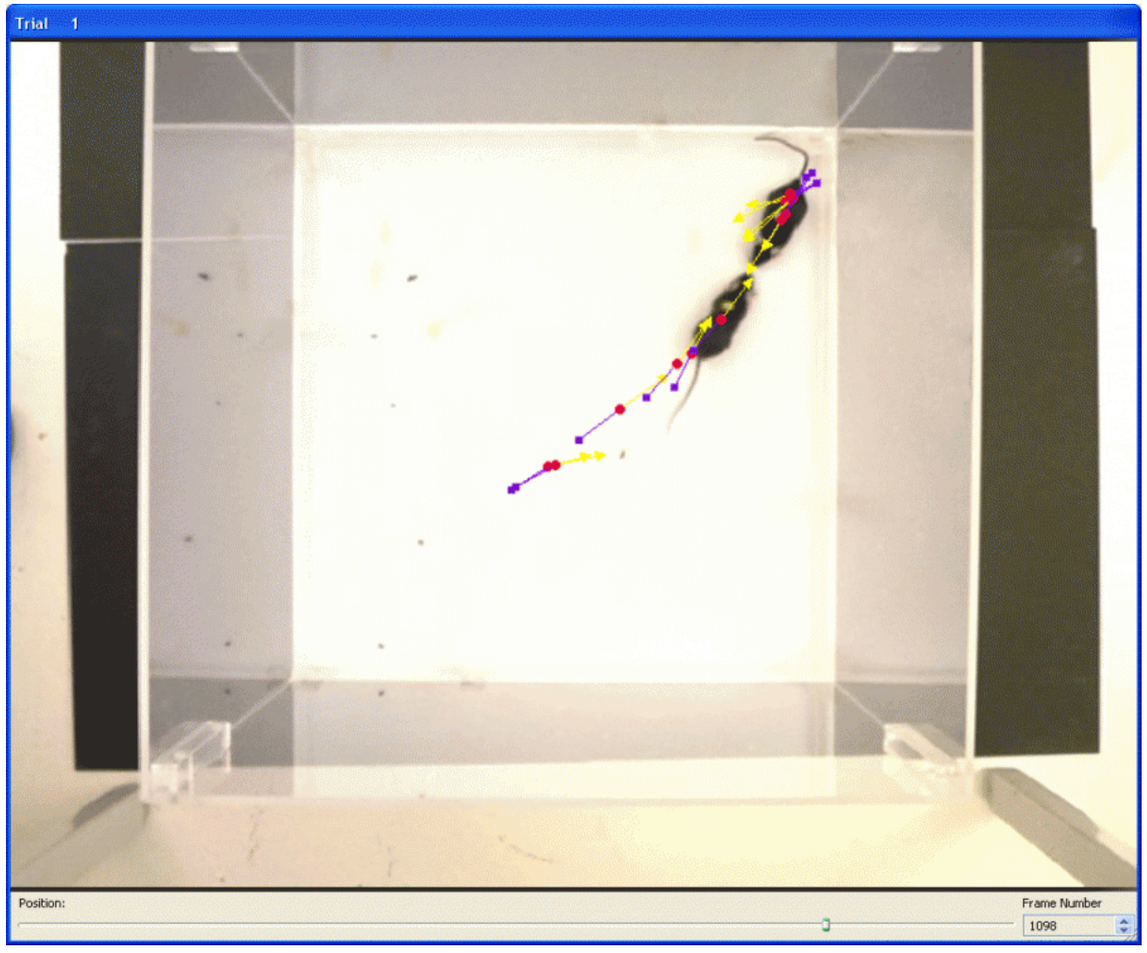
Light/ dark test



Animal model of normal anxiety
Based on social behavior



Social interaction test



- Measures the level of social behavior between unfamiliar animals in a aversive situation (lighted arena)

Animal model of normal anxiety
Based on social behavior

Social interaction test

Emotional behaviors coded in the social interaction test	
Freezing	Immobile and heightened rigid posture
Defensive posture	Posture with one or two front paws held close to the body or stretched out to maintain the other mouse at distance
Startle	Rapid and short- lasting jerks of the body
Kicking	Rapid extension and retraction of the rear paws
Vocalization	High- pitched, species- typical sounds
Escape	Running away
Jump	Upward movements with four paws
Aggression	Fight, bite, aggressive groom
Social investigation	Nonagonistic approach to other animal

Animal model of normal anxiety
Based on unconditioned responses

The Mouse Defense Test Battery

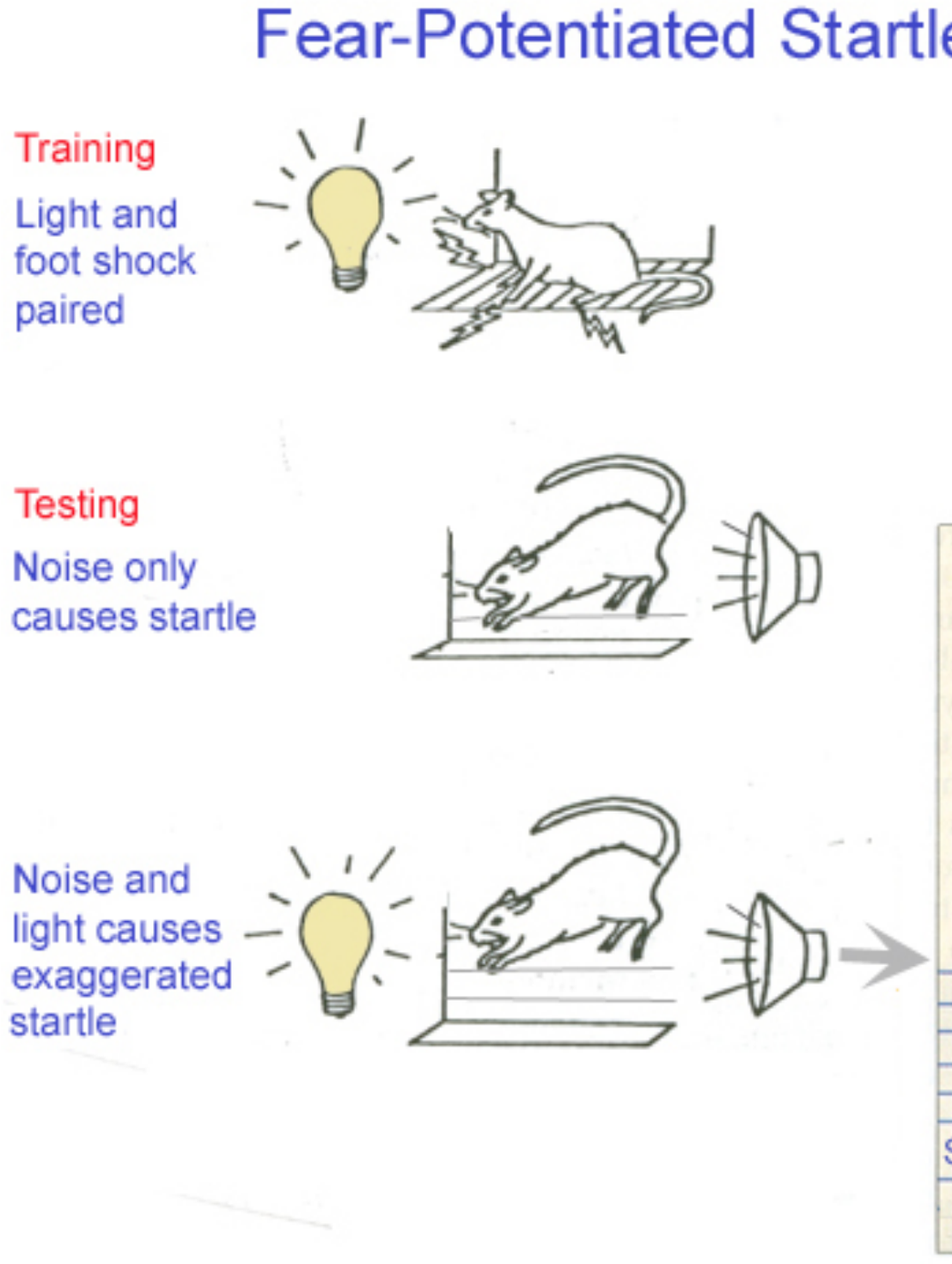
Animals are confronted with natural predators in an oval runway and behaviors associated with these threats are recorded

It measures risk assessment (stop and orientation when the mouse is chased), flight (avoidance distance), defensive threat and attack (vocalization, beating and upright posture) and contextual defense (escape attempts from the runway)

Animal model of normal anxiety
Based on conditioned behavior

Fear- potentiated startle test

- The amplitude of the startle response increases when light and noise are presented together and reflects both fear and anxiety



Animal model of pathological anxiety

Models for genetically- based anxiety

- Mice with mutation in single, distinct genes (5-HT1A receptor, CRF, gamma2 subunit of GABAA receptor, NPY)

- Rat or mouse lines selected on the basis of high or low emotional reactivity (BALB/c mouse strain, Wistar-Kyoto rat strain)

Animal model of depression

Type model	Sensitive to chronic drug treatment
Diathesis models: Lesion models Genomic models Genetic models Developmental models	Olfactory bulbectomy HPA axis transgenes Flinders sensitive line Prenatal or neonatal stress
Stress models: Acute stress Chronic stress	Learned helplessness Restraint stress Chronic mild stress Restraint stress
Social dominance models: Social separation Social defeat	Neonatal/adult isolation Resident- intruder Social hierarchy

Animal model of depression

The psychosocial stress model in male tree shrews (Tupaia belangeri)

Th

rews

TABLE 1. STRESS-INDUCED CHANGES IN MALE TREE SHREWS[23]

Physiological and Neuroendocrine Parameters	Effect of Chronic Psychosocial Stress
Body weight	5% to 10% decrease
Cortisol	Urinary cortisol: 2- to 5-fold increase (HPA-axis hyperactivity)
Adrenals	Increase
Testosterone	Decrease
Testes	Decrease
Sleep	Reduced slow-wave sleep, more/longer awake phases
Receptors in the Brain	
Hippocampal glucocorticoid receptors	Downregulation of GR; regional up- and downregulation of MR
CRH-receptors	Downregulation of binding sites for 125I-ovine CRH in anterior pituitary, dentate gyrus, CA1 and CA3 of the hippocampus, area 17, superior colliculus; upregulation of binding sites for 125I-ovine CRH in cortical regions, amygdala, choroid plexus
5-HT_{1A}-receptors	Gradual downregulation of heteroreceptors in hippocampus and cortical regions; fast renormalization after stress or hormonal replacement
α_1-adrenoceptors	Downregulation in brain regions involved in autonomic functions
β_1-adrenoceptors	After 4 weeks downregulation in hippocampus and parietal cortex; transient effects in prefrontal cortex, olfactory area, and pulvinar nucleus
β_2-adrenoceptors	After 4 weeks upregulation in pulvinar nucleus; transient effects in prefrontal cortex
Morphological changes in the brain	
Neurogenesis in the dentate gyrus	Inhibition of the proliferation of granule precursor cells
Retraction of dendrites	Retraction of apical dendrites of pyramidal neurons in the CA3 of the hippocampus
Volume of the hippocampal formation	Volume reduced by ~10%
Behavior	
General motor activity	Reduced
Self-grooming	Reduced
Scent-marking activity	Reduced
Feeding and water intake	Reduced

HPA=hypothamalic-pituitary-adrenal; GR=glucocorticoid receptors; MR=muscarinic receptors; CRH=corticotropin-releasing factor; 5-HT=serotonin.

Fuchs E. *CNS Spectr.* Vol 10, No 3. 2005.

Animal model of depression

The psychosocial stress model in male tree shrews (Tupaia belangeri)

TABLE 2. SIGNS AND SYMPTOMS OF MAJOR DEPRESSION (*DSM-IV* CRITERIA)[1] IN COMPARISON TO EFFECTS OF CHRONIC PSYCHOSOCIAL STRESS IN TREE SHREWS

DSM-IV Major Depression	Chronic Psychosocial Stress in Tree Shrews
Significant weight loss or weight gain when not dieting or decrease in appetite	Significant weight loss, reduced food and water intake
Insomnia or hypersomnia, early morning wakening	Disturbances in sleep patterns, early morning wakening
Marked diminished interest or pleasure in all or almost all activities most of the day, nearly every day	Reduced activity of the gonads
Depressed mood most of the day, as indicated either by subjective account or observation by others	Reduced locomotor activity and grooming behavior

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Fuchs E. *CNS Spectr.* Vol 10, No 3. 2005.

That's all Folks!