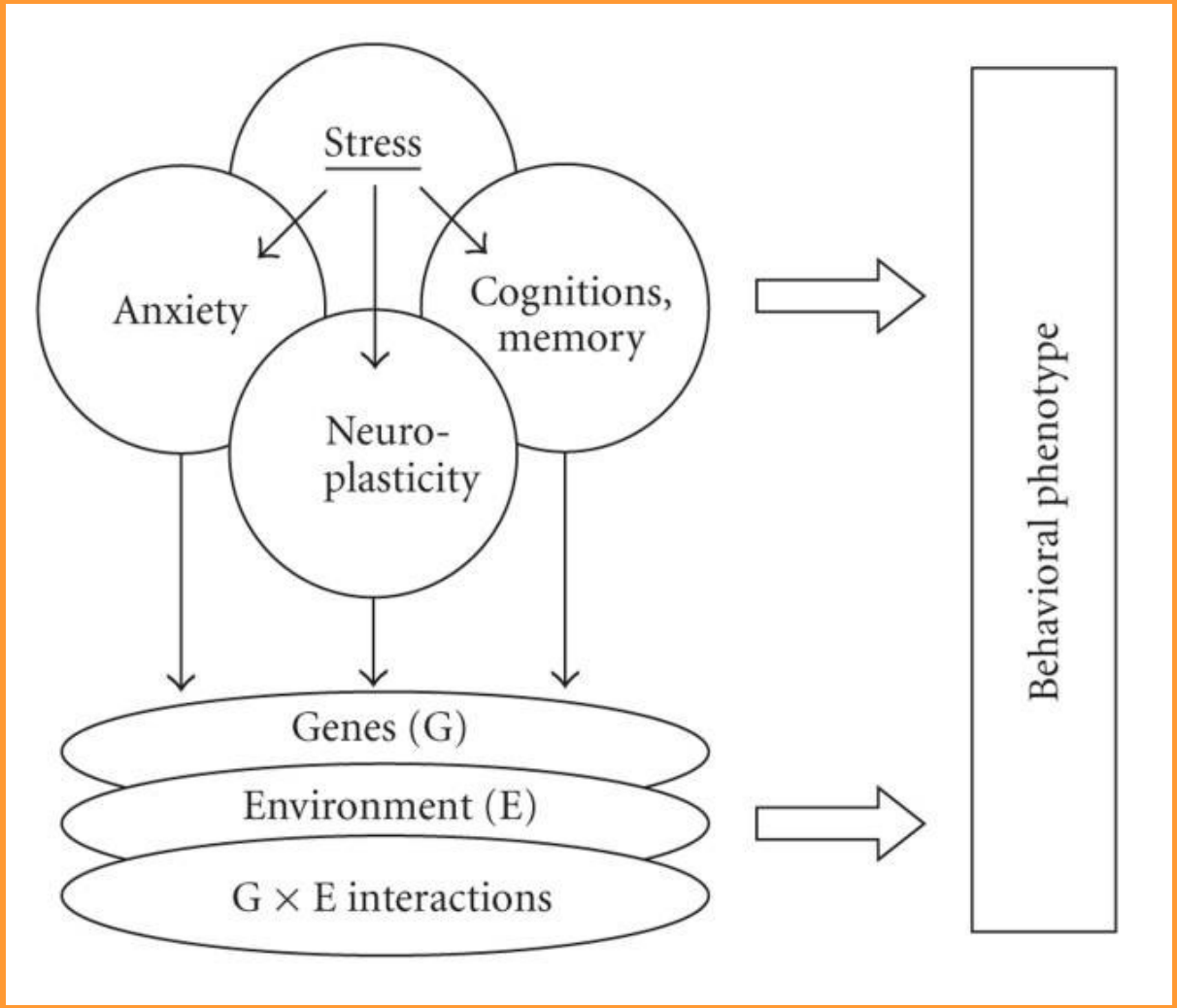
Cognitive Phenotypes

1st ISBS Summer School

St. Petersburg, Russia

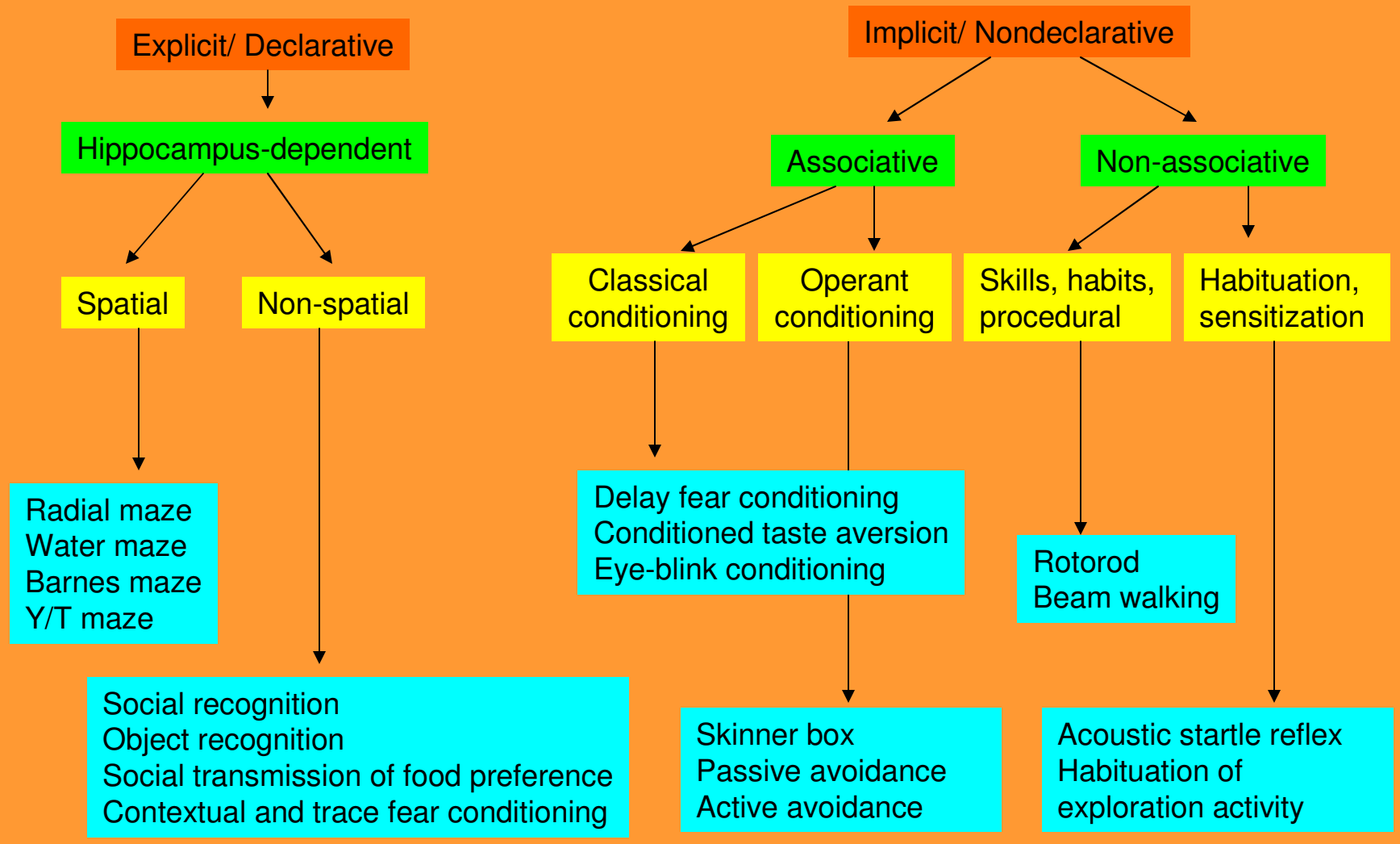
May 9th -15th,2008

Stress, memory, and anxiety interplay



Kalueff, 2007

Classification of memory procedures



Voikar, 2006

Spatial (hippocampal) cognitive tests

Barnes maze modifications

Neurodetective International, 2008

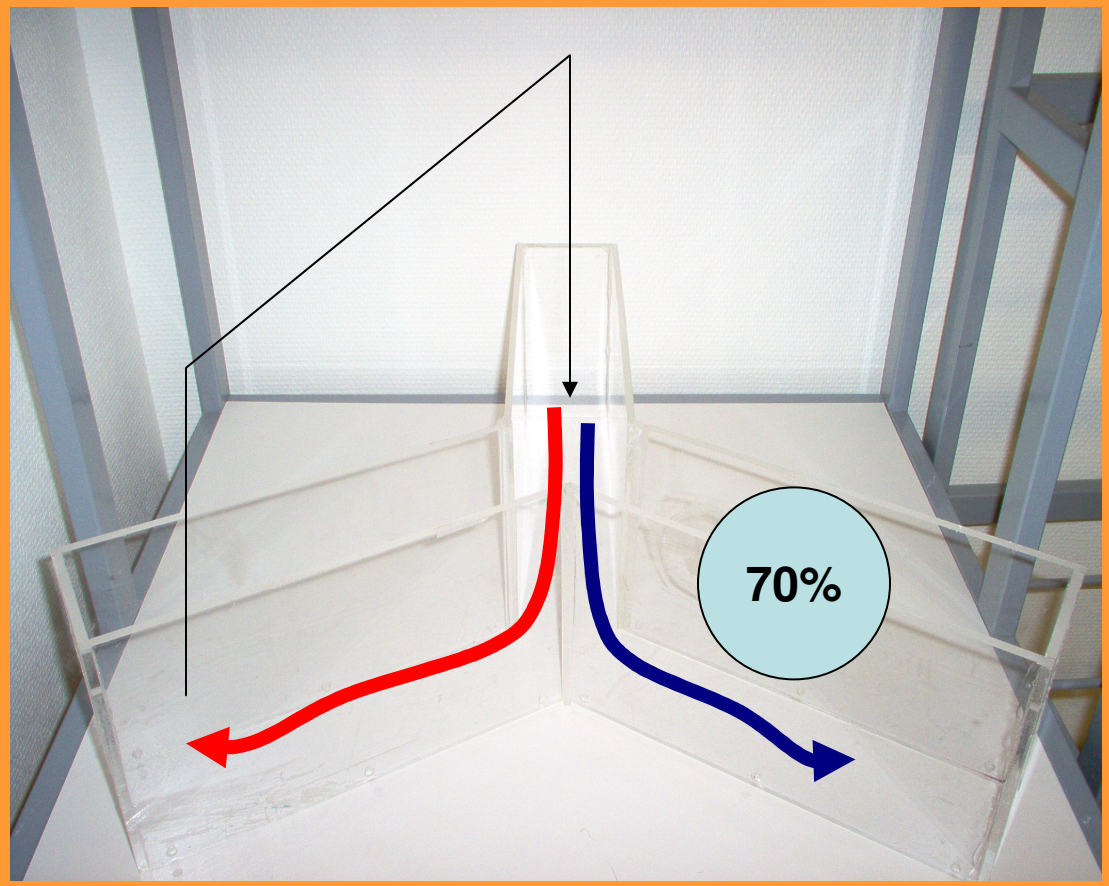
Spatial cognitive tests

- Radial maze (rat)
- Y-maze
- Watermaze place learning

Radial maze

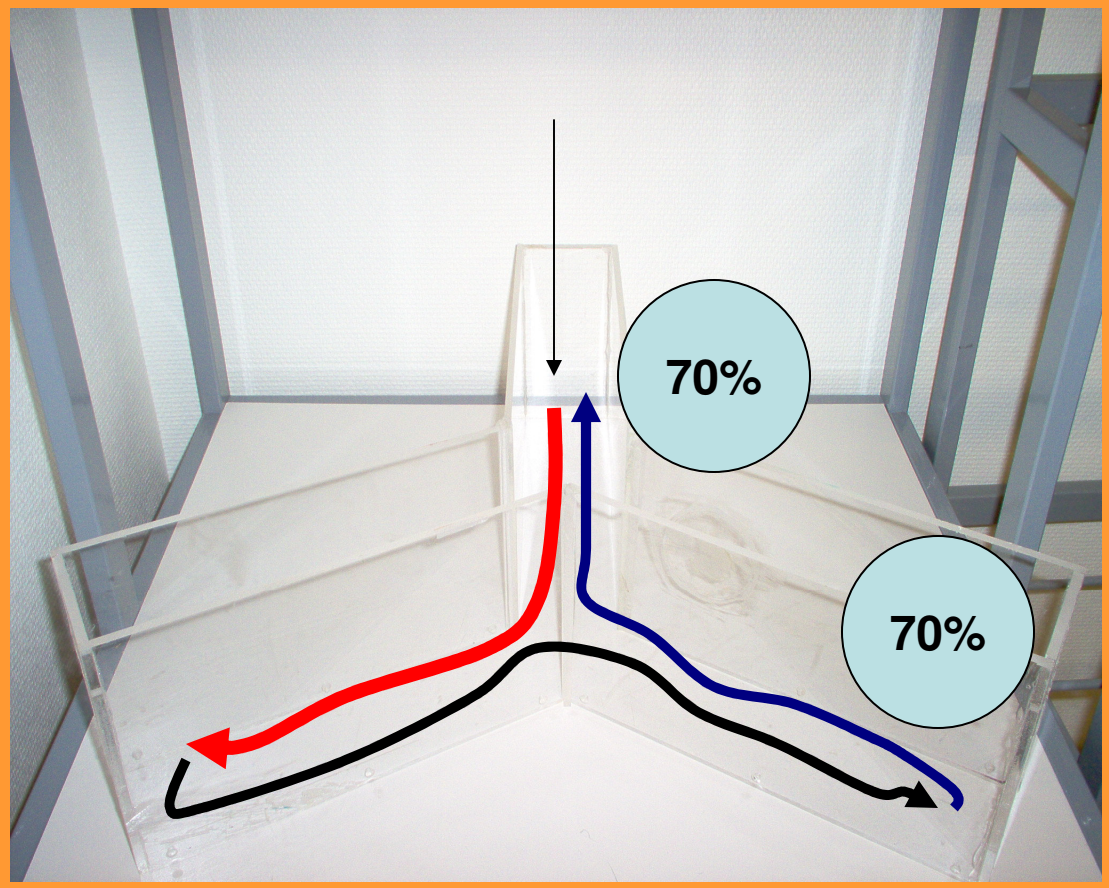
Neurodetective International, 2008

Spontaneous alternation (Y-maze)



Forced version, ≈10 trials
Sensitive: anxiety, inactivity

Spontaneous alternation (Y-maze)



Free exploration version, 1 trial, 5-10 min
Sensitive: anxiety, inactivity

Non-spatial cognitive tests

- Passive avoidance
- Social recognition

Associative memory tests

Conditioned taste aversion

- This paradigm pairs pleasant taste (saccharin) with i.p. injection of malaise-inducing agents
- Subsequent tests are then used to assess the animal's avoidance to the saccharine
- Suppression of saccharine drinking is a measure of associative learning
- This taste aversion is very robust and is generally acquired within a few trials

Crawley, 2000

Eye blink conditioning

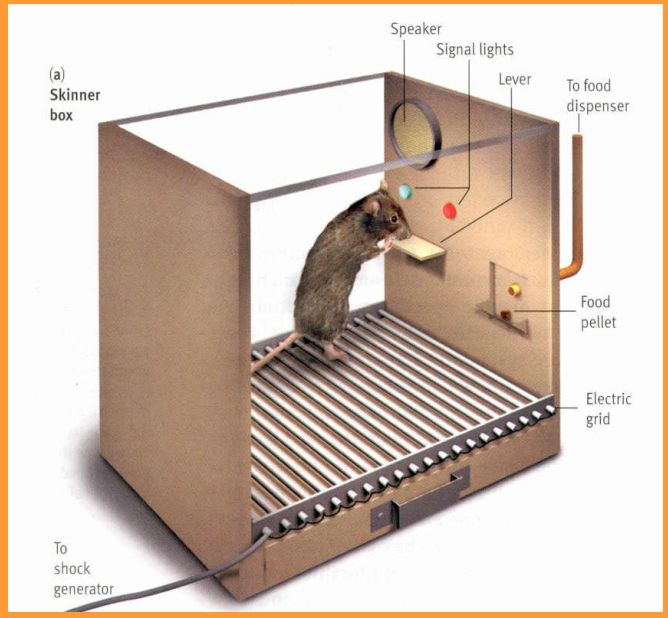
- A useful test for cerebellar motor learning
- 100-ms footshock is used as unconditioned stimulus
- An 80-dB tone is the conditioning stimulus
- Eye blink response is measured by electromyography from four subcutaneously placed electrodes

Crawley, 2000

Operant conditioning tests

Five-choice serial reaction time attention task

- The operant chamber has a series of nine holes and lights above each
- On each trial, one of five holes is illuminated for half a second and food is available at that hole for 5 seconds
- Each subsequent trial, one of the five is randomly lit and provides food
- The rodent must monitor 5 spatial locations simultaneously
- Accuracy and speed of responding are measures of the animal's attentional ability



http://iws2.ccccd.edu/lipscomb/16_week_course/images/Skinner_Box.jpg

Crawley, 2000

Non-associative memory

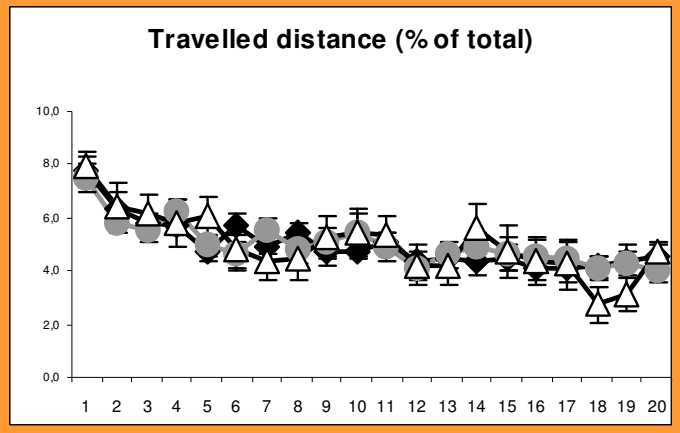
Spatio-temporal organization

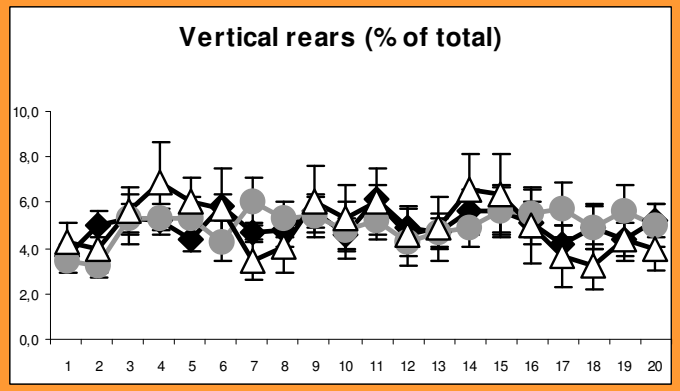
In addition to “amount” of behavior (frequency and duration measures), analyses of “quality” of behavioral represent an important part of behavioral phenotyping:

- spatial
- temporal
- spatio-temporal characteristics

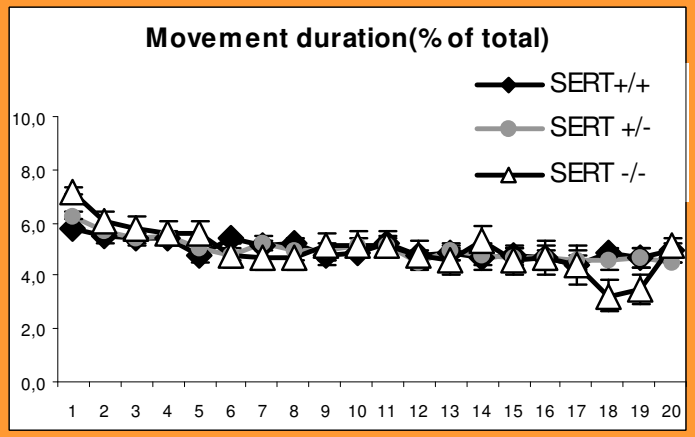
What? When? Where?

Within-trial Habituation: short-term (working) spatial memory





Time (min)

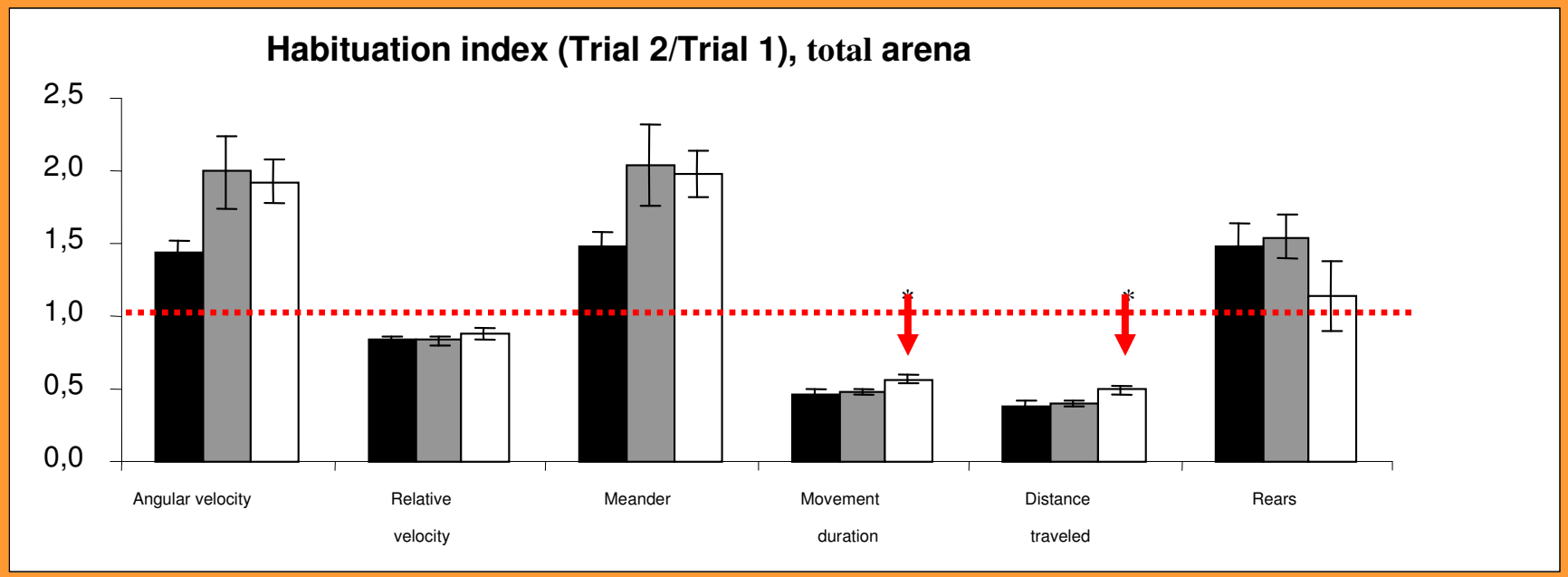


Time (min)

Spatial working memory is unaffected in SERT-/ mice

Kalueff et al., 2008

Between-trial habituation: Long-term spatial memory:



Long-term cognitive functions (such as spatial memory) are relatively normal in SERT-/- mice

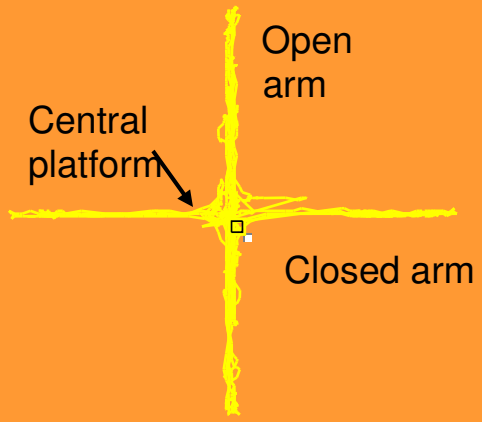
Kalueff et al., 2008

Elevated plus maze

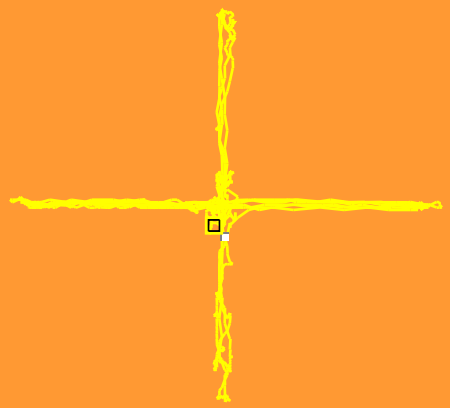
SERT-/-mice:

- **Increased anxiety**
- **Unaltered habituation (spatial memory)**
- **Unaltered long-term memory**
- **Increased turning behaviors**

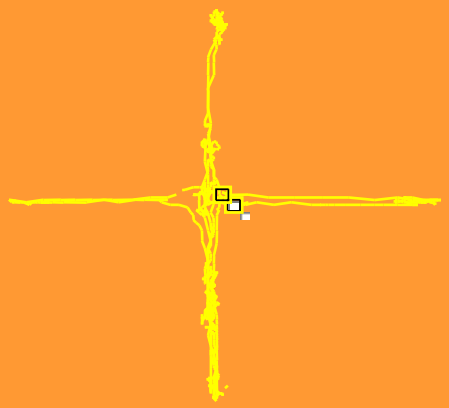
SERT+/+



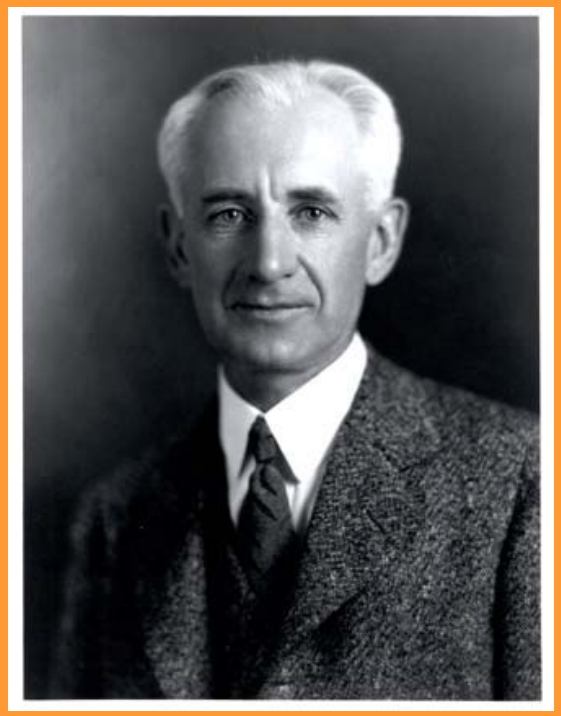
SERT+/-



SERT-/-



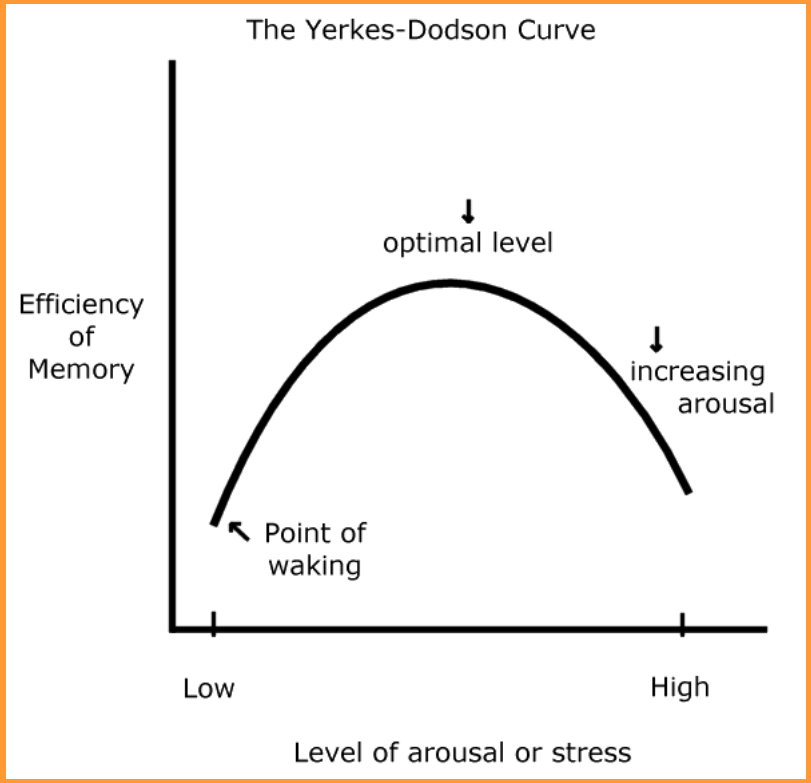
R. Yerkes



Robert M. Yerkes (1876-1956), a pioneer in psychology research. Received a Ph.D. in zoology from Harvard in 1902. From 1929 to 1944 he was Professor of Psychobiology at Yale Medical School. Yerkes directed the celebrated Laboratories of Primate Biology (Yerkes Laboratory) in New Haven and in Orange Park, Florida.

Yerkes-Dodson Law

- The empirical relationship between arousal and performance
- Developed by Robert M. Yerkes and J. D. Dodson in 1908
- Performance increases with physiological or mental arousal only to a point
- When arousal becomes too high, cognitive performance decreases
- Different tasks require different levels of arousal for optimal performance
- Because of task differences, the shape of the curve can be highly variable



Memory and anxiety interplay

Domains		**Anxiety**	
Memory, learning	**Elevated**	**Unaltered**	**Reduced**
Elevated	Likely phenotype: ↑ initial anxiety (↓ activity) with ↑ habituation (anxiolytics would ↓ hypoactivity and habituation). Possible misinterpretation of baseline phenotype: hyperanxiety; ↓ sensitivity to repeated stressors (while, in fact, having ↑ vulnerability to chronic stress)	Likely phenotype: ↑ habituation [anxiolytics would ↑ activity and ↓ habituation]. Possible misinterpretation: ↓ exploration (↑ anxiety). Anxiolytics would ↓ habituation (however, this may be mistaken for ↓ anxiety)	Likely phenotype: ↓ initial anxiety with ↑ habituation (anxiolytics would ↓ habituation) Possible misinterpretation: initial hyperactivity followed by ↑ freezing ("↑ anxiety"). Anxiolytics will ↓ habituation (however, this may be mistaken for mild psychostimulant action)
Unaltered	Likely phenotype: ↑ anxiety (↓ exploration), normal memory. Anxiolytics may ↓ anxiety and memory. In some tests phenotype may be misinterpreted as baseline hypolocomotion		Likely phenotype: reduced anxiety (↑ exploration), normal memory. Anxiolytics may impair memory without affecting (already low) anxiety In some tests baseline phenotype may be misinterpreted as hyperactivity
Reduced	Likely phenotype: ↑ initial anxiety with ↓ habituation. Anxiolytics may ↓ anxiety and further impair memory. Possible misinterpretation of baseline phenotype: hypersensitivity to repeated stressors (while, in fact, having ↓ vulnerability to chronic stress). Effects of anxiolytics may be mistaken for psychostimulant action	Likely phenotype: ↓ habituation. Anxiolytics may further impair memory. Possible misinterpretation of baseline phenotype: ↑ exploration (↓ anxiety). Effects of anxiolytics may be mistaken for psychostimulant action	Likely phenotype: ↓ initial anxiety with ↓ habituation (anxiolytics may ↓ memory). In some tests may be misinterpreted as persistent hyperlocomotion. Effects of anxiolytics may be mistaken for psychostimulant action

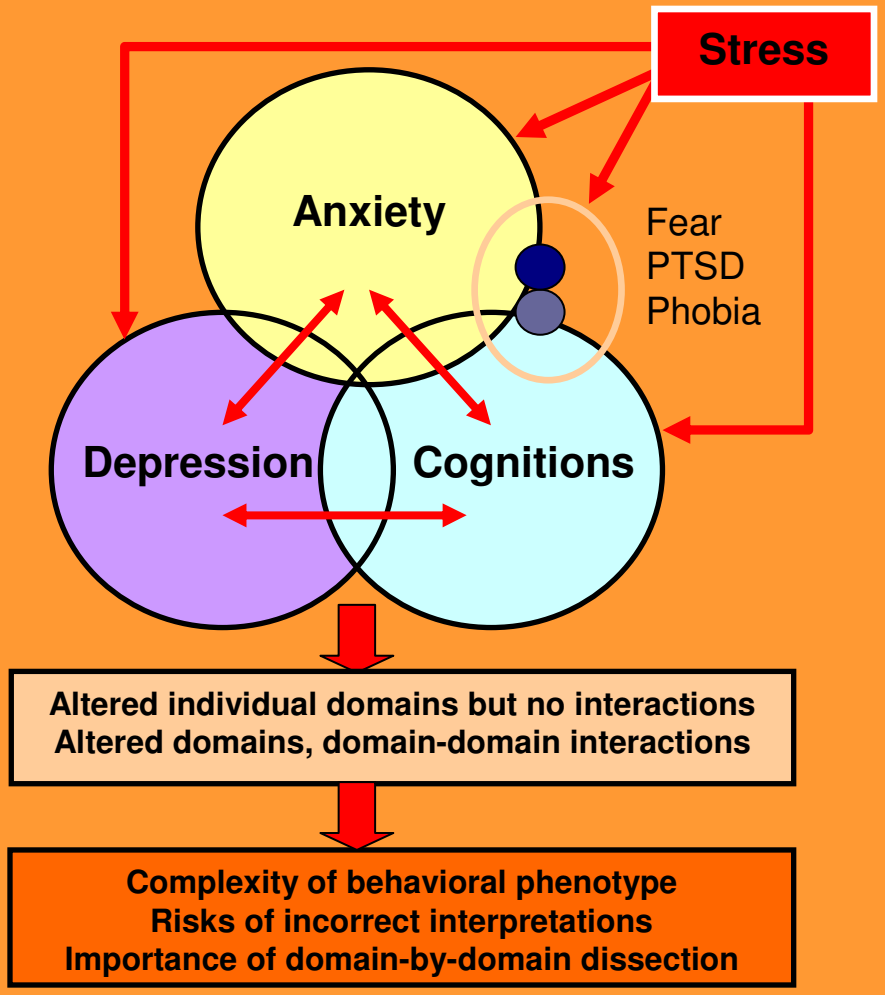
Kalueff and Murphy, 2007

Memory and depression interplay

Domains		**Depression**	
Memory, learning	**Elevated**	**Unaltered**	**Reduced**
Elevated	Likely phenotype: hypoactivity (or stereotypic hyperactivity in some tests) but ↑ sensitivity to repeated stressors. Possible misinterpretation of baseline phenotype: ↑ anxiety/freezing (or ↓ habituation, spatial memory in acute stress models)	Likely phenotype: ↑ habituation and ↑ sensitivity to repeated stressors. Possible misinterpretations: ↓ exploration (↑ anxiety) and ↑ despair depression	Likely phenotype: active locomotion with ↑ habituation and sensitivity to repeated stressors. Possible misinterpretations: initial hyperactivity followed by gradually ↑ anxiety, or ↑ "despair" depression (which, in fact, reflects ↑ learning)
Unaltered	Likely phenotype: ↓ hypoactivity (or stereotypic hyperactivity in some tests). Possible misinterpretation: ↑ anxiety/freezing (or ↓ habituation, spatial memory)		Likely phenotype: active locomotion. Possible misinterpretation of this phenotype: no or ↓ anxiety
Reduced	Likely phenotype: marked sustained hypoactivity (or stereotypic hyperactivity) with ↓ habituation and sensitivity to repeated stressors. Possible misinterpretations: ↑ anxiety (and/or OCD-like behavior) or ↓ despair depression	Likely phenotype: ↓ habituation. Possible misinterpretation: ↑ exploration (↓ anxiety)	Likely phenotype: active locomotion with ↓ habituation and sensitivity to repeated stressors. In some tests this may be misinterpreted as persistent hyperlocomotion

Kalueff and Murphy, 2007

The importance of assessment of cognitive phenotypes



"Can my findings be a result of altered memory or learning?" - should be one of the first questions asked in studies on animal emotionality and affective behaviors


© Original Artist
Reproduction rights obtainable from
www.CartoonStock.com
Dave Carpenter...
"OKAY, HERE'S THE PLAN..."