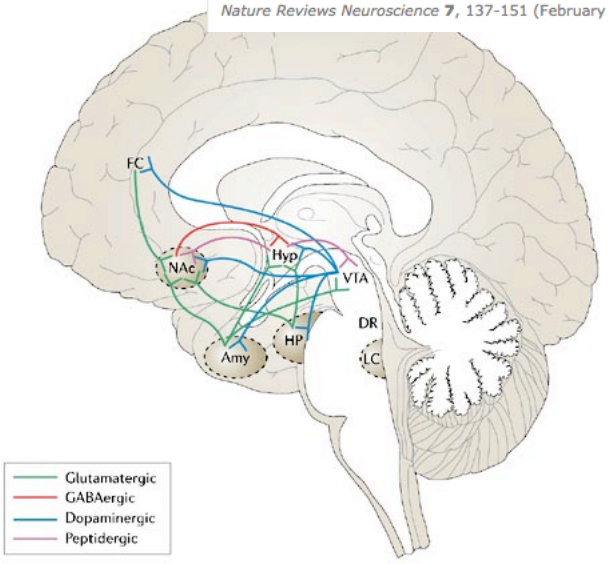
New approaches to antidepressant drug discovery: beyond monoamines

Olivier Berton & Eric J. Nestler

Nature Reviews Neuroscience **7**, 137-151 (February 2006)



Human circuitry of depression

(peptidergic = endorphins, enkephalins, etc)

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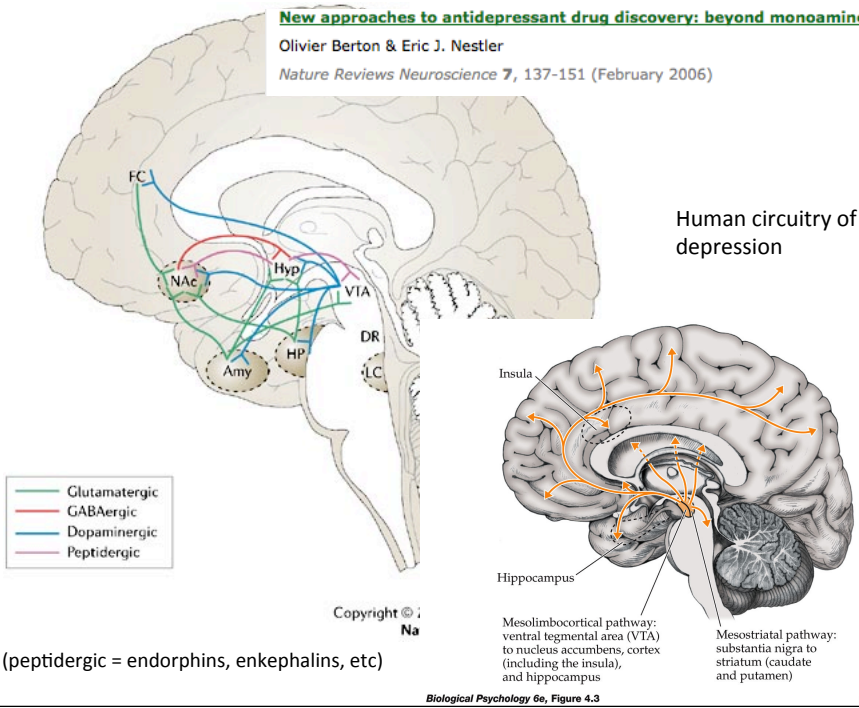

Human circuitry of depression

(peptidergic = endorphins, enkephalins, etc)

Biological Psychology 6e, Figure 4.3

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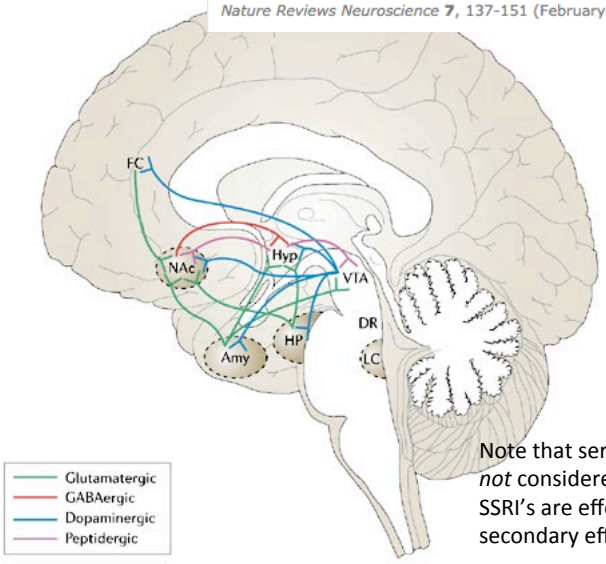


Human circuitry of depression

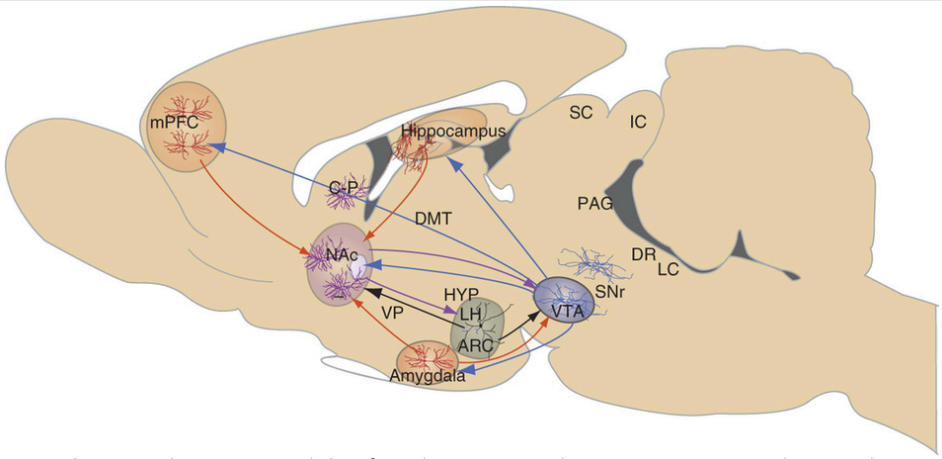
Note that serotonin systems are *not* considered primary, although SSRI's are effective ADs – possibly via secondary effects on other systems

(peptidergic = endorphins, enkephalins, etc)

Figure 3: Brain circuitry implicated in resilience to depression and anxiety disorders.

From
Neurobiology of resilience
Scott J Russo, James W Murrough, Ming-Hu Han, Dennis S Charney & Eric J Nestler

Rodent circuitry of "depression"



NA nuclues accumbens, mPFC medial prefrontal cortex, CP caudate putamen, VTA ventral tegmenal area, DMT dorsal medial thalamus, SC/IC superior/inferior colliculus, VP ventral pallidum, SN substantia nigra, ARC arcuate nucleus, LH lateral hypothalamus, LC locus coerouleus

Glutamate=red, GABA=purple, Peptidergic=black, dopamine=blue

Genetic Mouse Models of Depression

Christopher Barkus

A good rodent model of depression would feature many of the depressive-like behaviours detailed below, as well as possibly some of the associated physiological changes commonly seen in depressed individuals, such as altered EEG sleep architecture. When the depressive-like phenotype detected in a mutant mouse model can also be reversed by clinically effective antidepressants, this adds to the validity of the model.

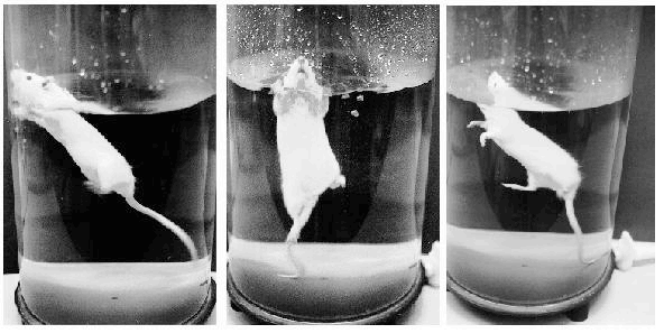
To avoid suggesting we can measure mood *per se* in rodents, the term "behavioural despair" is often applied to tests sensitive to antidepressant treatment. The two most commonly used tests for behavioural despair in mice are the forced swim test and the tail suspension test.

Are you:

- ☐ Feeling sad or guilty often
- ☐ Not enjoying daily activities
- ☐ Eating or sleeping more, or less
- ☐ Feeling irritable or tired
- ☐ Having trouble with concentration or memory
- ☐ Thinking about suicide

Forced Swimming

(also called "behavioral despair" test)

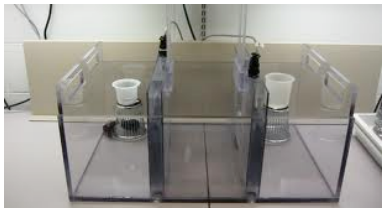


Swimming | Struggling | Floating

Tail suspension

Other tests:

Anhedonia: sucrose preference, social interaction



Anxiety: Plus maze, thigmotaxis in open field

Circadian and sleep disruptions

- Mouse models (from Barkus chapter)
  - Low expressing variant of gene for 5HT transporter/5HT KO mice
  - A2a adrenoreceptor (NE) KO mice
  - Noradrenaline (NE) transporter KO mice
  - CRF models (corticotropin releasing factor from hypothalamus)
  - BDNF models

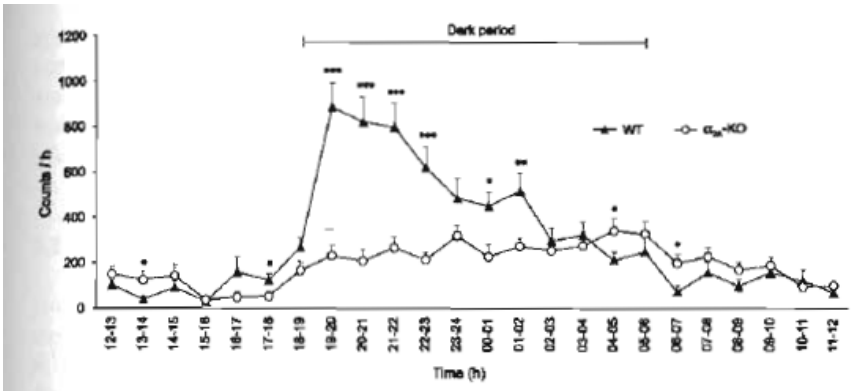
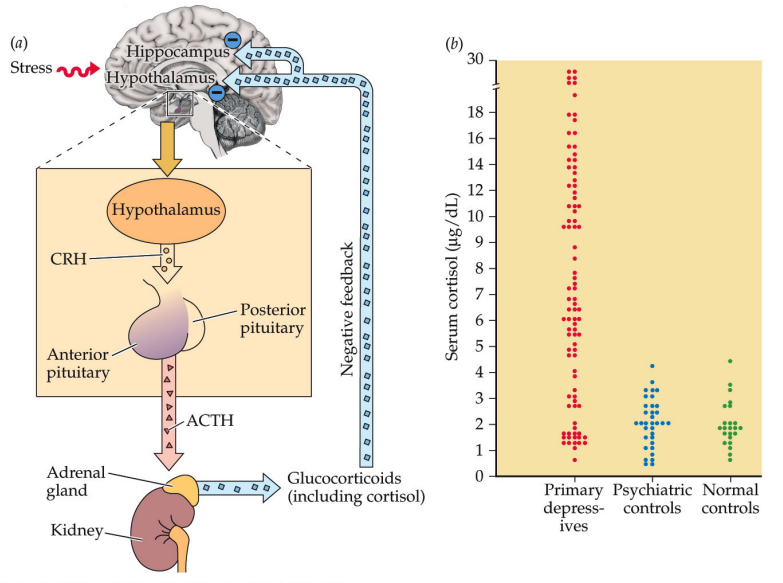
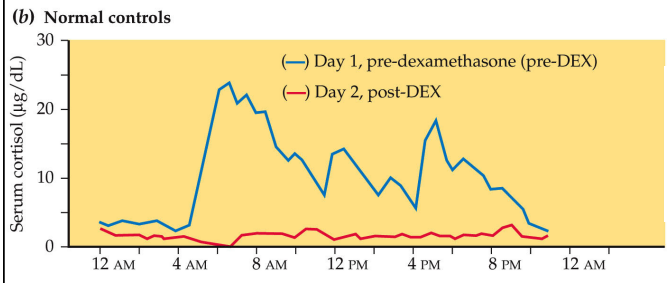


Fig. 1 The locomotor activity of wild type and α_{2A} adrenoceptor knoekout mice over a 24 h period following a 2 h habituation period. Wild-type mice show a dramatic increase in loeomotor activity in response to the onset of the dark period of the diurnal cycle but this is absent in α_{2A} adrenoceptor knockout mice. This may be relevant to the disruption of circadian rhythms seen during a depressive episode (from Lahdesmaki et al. 2002)

Higher cortisol (stress) levels in depressed individuals.

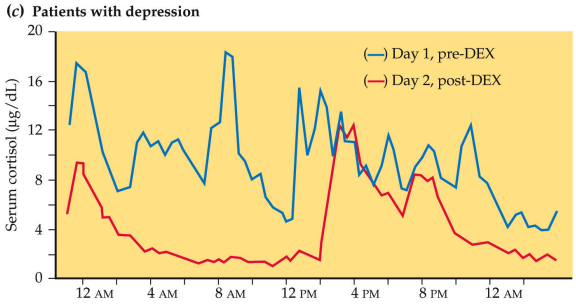


***Biological Psychology 6e*, Figure 16.14 (Part 1)**

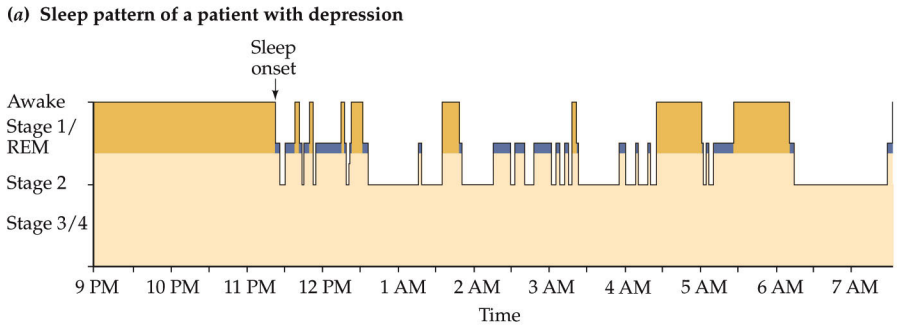


In *normal controls*, dexamethasone (a synthetic cortisol-like glucocorticooid) leads to feedback inhibition of cortisol.

In *depressed patients*, dexamethasone seems less able to produce feedback inhibition of cortisol (a faulty H-P-A system?)



***Biological Psychology 5e*, Figure 16.13 (Part 3)**



Depressed patients spend little/no time in deep (stage 3/4) sleep (could reflect the fact that cortisol levels normally *fall* during the night and *rise* just before we wake up, but may *remain* elevated in depressed patients). Elevated REM?

Other considerations to interpreting mouse model data:

- Sex
- Environment
- Employment of task parameters (e.g., duration of pre-swim)
- Background strain (e.g., C57 that can climb up tail makes poor background strain for tail suspension task)

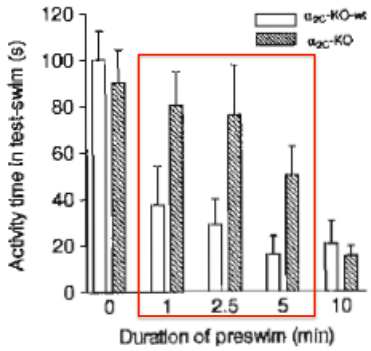


Fig. 2 The time spent active during a 5 min forced swim test following various lengths of prior exposure 24 h previously in wild type and α_{2C} adrenoceptor knockout mice. Prior exposure to forced swimming reduces activity in mice. In the case of this study, this effect was more dramatic in wild-type mice and so revealed an anti-depressive-like phenotype in α_{2C} adrenoceptor knockout mice. This suggests the use of a pre-swim session may be important in determining the sensitivity of the forced swim test. Taken from Sallinen et al. (1999)

The Flinders Sensitive Line Rat Model of Depression—25 Years and Still Producing

David H. Overstreet and Gregers Wegener

The Flinders sensitive line (FSL) rat has been purported to be a genetic animal model of depression because of several features that resemble human depressives, including elevated rapid eye movement (REM) sleep and an exaggerated swim test immobility that can be reduced by chronic antidepressant treatments. Previous reviews

It must be emphasized that we had no intention of creating an animal model of depression. The original intent of our work was to create a strain of rat that was resistant to the anticholinesterase agent, diisopropyl fluorophosphate (DFP). The mechanisms underlying this resistance were to be compared with those previously established for rats that became tolerant to DFP following chronic treatment (Russell et al., 1982; Russell and Overstreet, 1987). However, the selective breeding program did not result in a resistant strain of rat; instead, a strain of rat that became progressively more sensitive to DFP was established, with the other strain, sometimes called the Flinders resistant line (FRL), resembling control Sprague-Dawley (SD) rats (Overstreet et al., 1979b).

Possible anti-depressants (AD)

Drugs that have elicited an AD-like effect in the FSL rat after chronic treatment

Drug (mg/kg)	Dose	Drug Class	Change in Swimming	References
Desipramine	5	Tricyclic	Significant increase	Pucilowski and Overstreet, 1993
Desipramine	5	Tricyclic	Significant increase	Schiller et al., 1992
Desipramine	5	Tricyclic	Significant increase	Zangen et al., 2001
Sertraline	5.7	SSRI	Significant increase	Pucilowski and Overstreet, 1993
Imipramine	15	Tricyclic	Significant increase	Schiller et al., 1992
DFP	1	Anticholinesterase	No Change	Schiller et al., 1992
SSR125543	3, 30	CRF1 antagonist	Significant increase	Overstreet and Griebel, 2004[a]
SSR58611A	1, 3	β2 NA agonist	Significant increase	Overstreet et al., 2008[a]
Nemifitide	0.3	Analog of MIF	Significant increase	Overstreet et al., 2004a[a]
Amphetamine	2	Stimulant	No change	Overstreet et al., 1995
Scopolamine	2	Anticholinergic agent	No change	Overstreet et al., 1995
SSR149415	10, 30	V1b antagonist	Significant increase	Overstreet and Griebel, 2005
CP154,526	10 × 2	CRF1 antagonist	Significant increase	Overstreet et al., 2004b[a]
Citalopram	5, 10	SSRI	Significant increase	Overstreet et al., 2004b[a]
Saredutant	1, 10	NK2 antagonist	Significant increase	Overstreet et al., 2010a[a]
Paroxetine	7.5	SSRI significant	Increase	Mork et al., 2011
Paroxetine	7.5	SSRI	Significant increase	Zangen et al., 2001
Ondansetron	1, 10	5-HT_3 antagonist	Significant increase	Mork et al., 2011
Lu AA33810	3, 10	NPY Y5 antagonist	Significant increase	Walker et al., 2009
S 20304	1, 20	Melatonin agonist	Significant increase	Overstreet et al., 1998a
S 20928	1, 10	Melatonin antagonist	No change	Overstreet et al., 1998a
Inositol	1200	Precursor to inositol	Significant increase	Einat et al., 2002
Nicotine	0.4	Nicotine agonist	Significant increase	Tizabi et al., 1999
NGF	Many	Trophic factor	Significant increase	Overstreet et al., 2010b

Note that all drugs show efficacy only after chronic treatment (14 days+) in the FSL model. Also, the FSL model does not show the anhedonia aspect of depression models.

Research Report

Pitx3 deficient mice as a genetic animal model of co-morbid depressive disorder and parkinsonism

Kyoung-Shim Kim[a,*,1], *Young-Mi Kang*[a,1], *Young Kang*[a], *Tae-Shin Park*[a], *Hye-Yeon Park*[a], *Yoon-Jung Kim*[a], *Baek-Soo Han*[b], *Chun-Hyung Kim*[d], *Chul-Ho Lee*[a], *Paul A. Ardayfio*[c], *Pyung-Lim Han*[e], *Bong-Hyun Jung*[f], *Kwang-Soo Kim*[d,**]

ABSTRACT

Approximately 40-50% of all patients with Parkinson's disease (PD) show symptoms and signs of depressive disorders, for which neither pathogenic understanding nor rational treatment are available. Using Pit3x-deficient mice, a model for selective nigrostriatal dopaminergic neurodegeneration, we tested depression-related behaviors and acute stress responses to better understand how a nigrostriatal dopaminergic deficit increases the prevalence of depressive disorders in PD patients. Pitx3-deficient mice showed decreased sucrose consumption and preference in the two-bottle free-choice test of anhedonia. Acute restraint stress increased c-Fos (known as a neuronal activity marker) expression levels in various brain regions, including the prefrontal cortex, striatum, nucleus accumbens, and paraventricular nucleus of the hypothalamus (PVN), in both Pitx3+/+ and −/− mice. However, the stress-induced increases in c-Fos levels in the cortex, dorsal striatum, and PVN were significantly greater in Pitx3−/− than +/+ mice, suggesting that signs of depressive disorders in parkinsonism are related to altered stress vulnerability. Based on these results, we propose that Pitx3 −/− mice may serve as a useful genetic animal model for co-morbid depressive disorder and parkinsonism.

HYPERACTIVITY

- often fidgets with hands or feet or squirms in seat
- often leaves seat in situations in which staying seated is expected
- often runs about or climbs excessively in inappropriate situations
- in adolescents or adults, may be limited to feelings of restlessness
- often has difficulty playing or engaging in leisure activities quietly
- is often "on the go" or often acts as if "driven by a motor"
- often talks excessively

IMPULSIVITY

- often blurts out answers before questions have been completed
- often has difficulty awaiting turn
- often interrupts or intrudes on others (conversations, games)

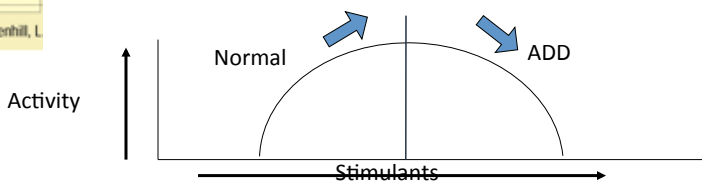
INATTENTION

- often fails to give close attention to details
- often has difficulty sustaining attention in tasks or play activities
- often makes careless mistakes in schoolwork, work, or other activities
- often does not seem to listen when spoken to directly
- often does not follow through on instructions
- often fails to finish schoolwork, chores, or duties in the workplace
- not due to oppositional behavior or failure to understand instructions
- often has difficulty organizing tasks and activities
- often avoids or dislikes tasks that require sustained mental effort
- often loses things necessary for tasks (assignments, pencils, books, etc.)
- is often easily distracted by extraneous stimuli
- is often forgetful in daily activities

Medication
Amphetamines
Short Acting:
Dexedrine
Adderall
Long Acting:
Dexedrine Spansule
Adderall XR
Methylphenidates
Short Acting:
Ritalin
Focalin
Long Acting:
Ritalin SR
Metadate CD
Concerta

Source: Adapted from Greenhill, L.

Paradoxical calming effects of stimulants (increase epinephrine and dopamine) on individuals with ADD/ADHD.



(Increasing levels of D and E)

Strengths and limitations of genetic models of ADHD

Raul R. Gainetdinov

Table 1 Summary of observations in DAT mutant models with regard to ADHD-related phenotypes

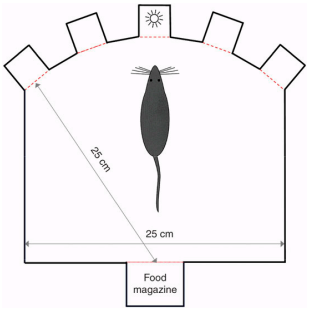
Mice	DAT expression (%)	Extracellular DA (%)	Locomotor activity	Responses to psychostimulants
DAT-KO	0	500	Extreme hyperactivity	Amphetamine and methylphenidate inhibit hyperactivity
DAT knockdown	10	200	Moderate hyperactivity	Amphetamine inhibits hyperactivity
DAT heterozygous	50	200	Normal	Reduced stimulation after amphetamine
DAT siRNA	60	N.D.	Normal	Reduced stimulation after amphetamine
Wild type	100	100	Normal	Normal stimulation after amphetamine and methylphenidate
Transgenic DAT overexpression	130	N.D.	Hypoactivity in a novel environment	N.D.
BAC DAT overexpression	300	60	Normal	Markedly enhanced amphetamine stimulation

Detailed description of these mutant models and respective references are presented in the text

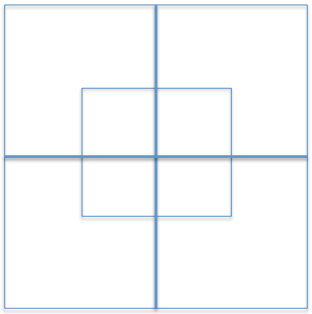
N.D. not determined

Reinforcement, Dopamine and Rodent Models in Drug Development for ADHD

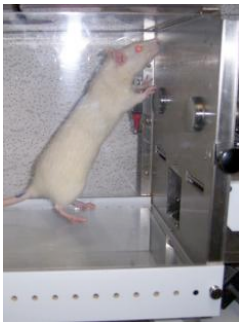
Gail Tripp · Jeff Wickens



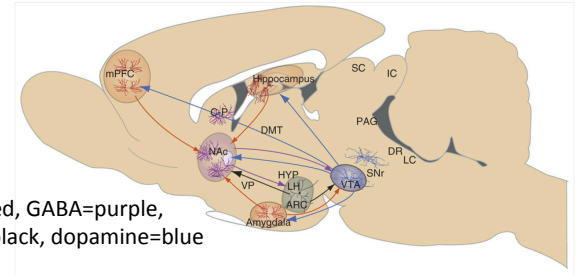
Attention/vigilance
5CSRT



Locomotion/hyperactivity
Open Field

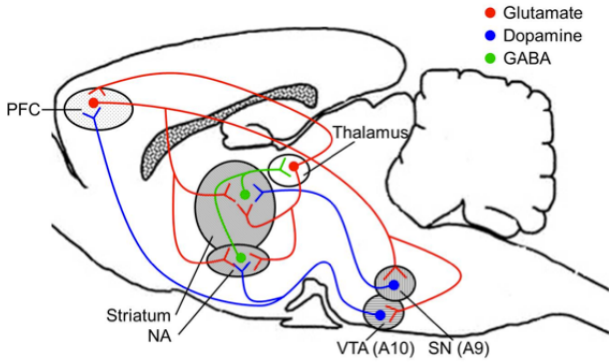


Impulsivity/
Response inhibition failure
Delay discounting



Glutamate=red, GABA=purple,
Peptidergic=black, dopamine=blue

Depression



Attention