行为的遗传控制

行为(Behavior)：生物体对内外环境的变化或信号刺激所作出一种生理反应。按其决定因素可分为：

- 先天性行为（本能性行为）

—— 动物生来就有的，主要是先天遗传因素决定的。包括性行为（sexual behavior），情绪行为（emotional behavior）和动机行为（motivated behavior）。

- 后天性行为（习得性行为）

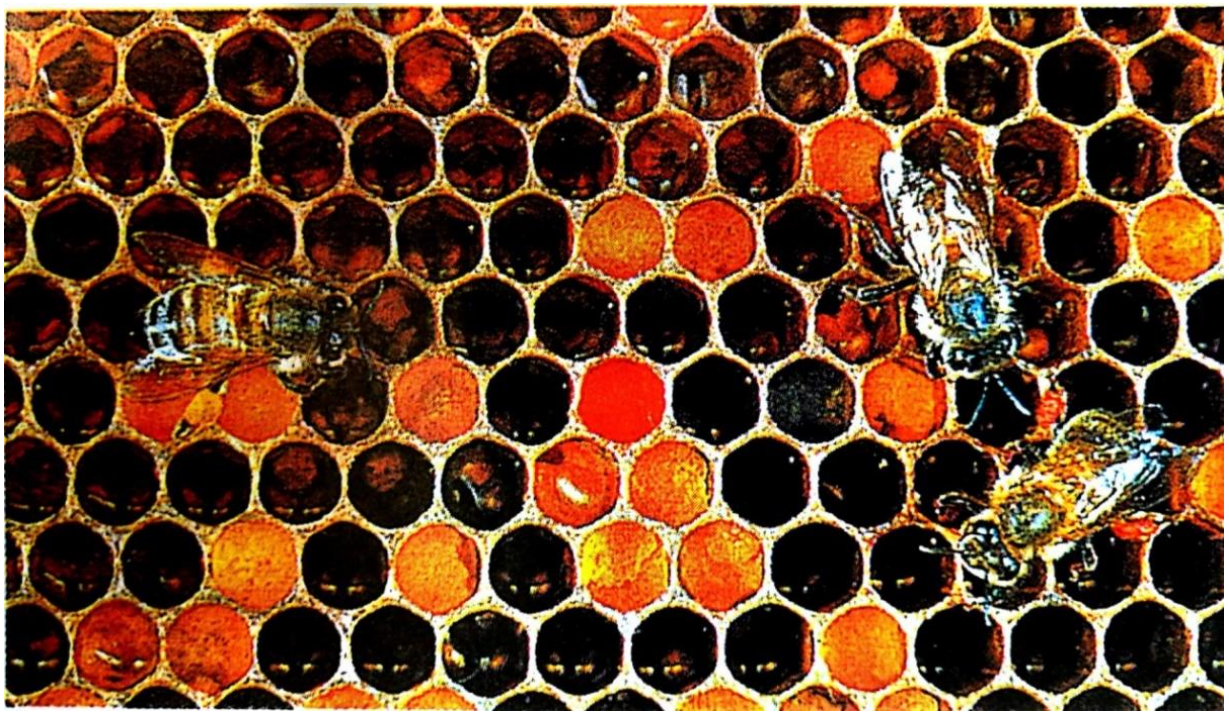
—— 动物在生长过程中，通过积累生活经验和“学习”逐渐建立起来的新的行为。

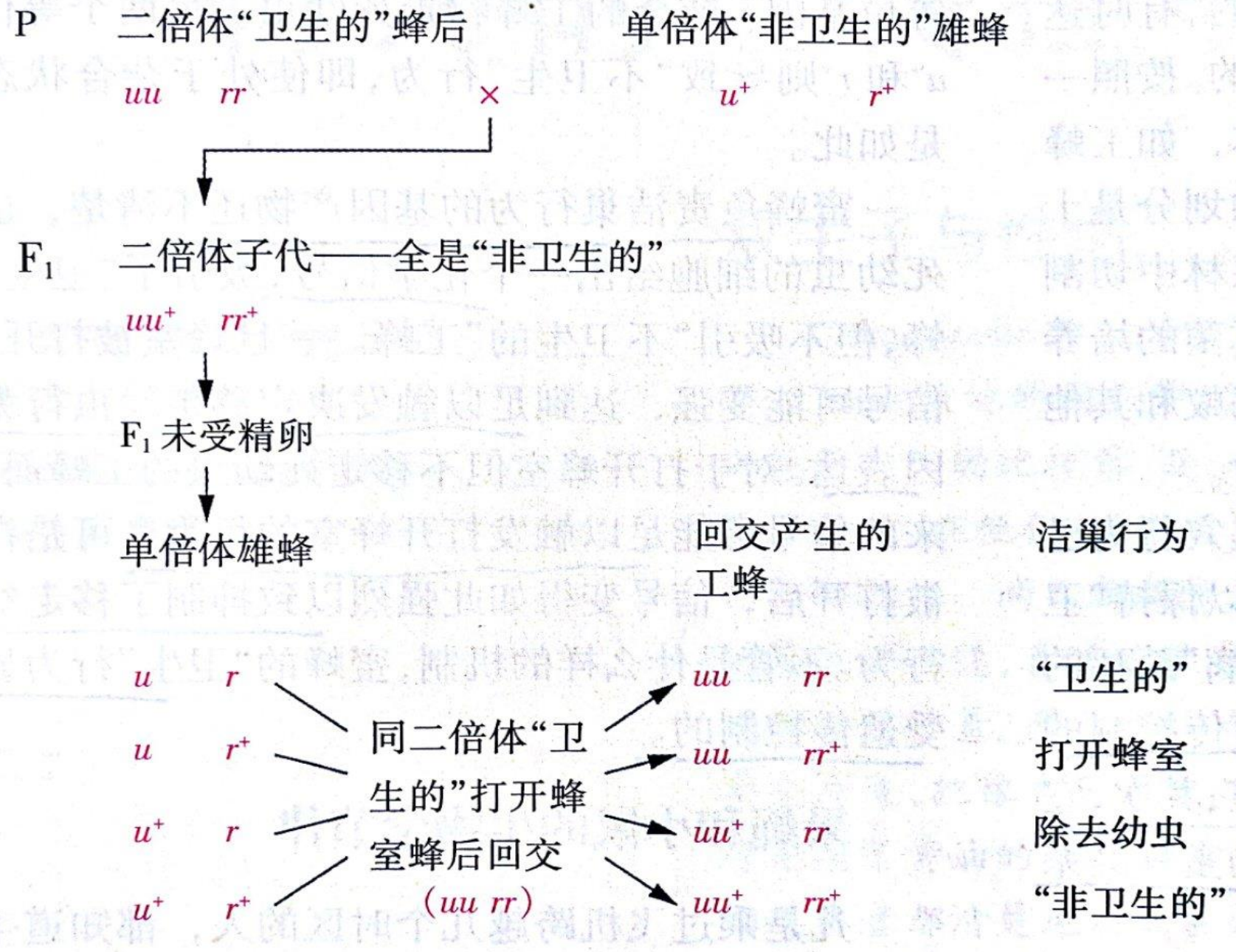
讨论问题：

- 动物行为的遗传分析
- 遗传变异对人类行为的影响

一、实验动物行为的遗传分析

1. 蜜蜂的洁巢行为：**工蜂清除封盖巢房中的虫蛹尸体的行为；**

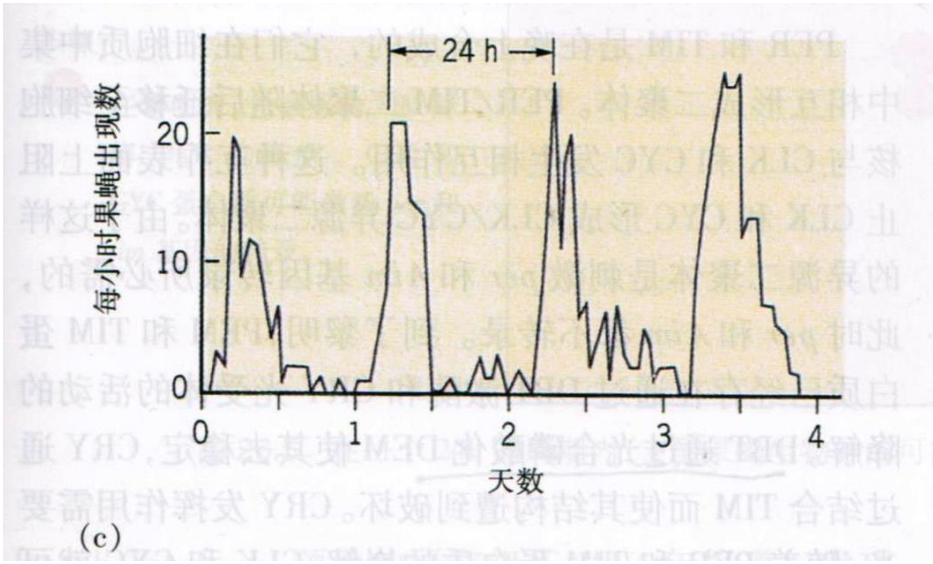


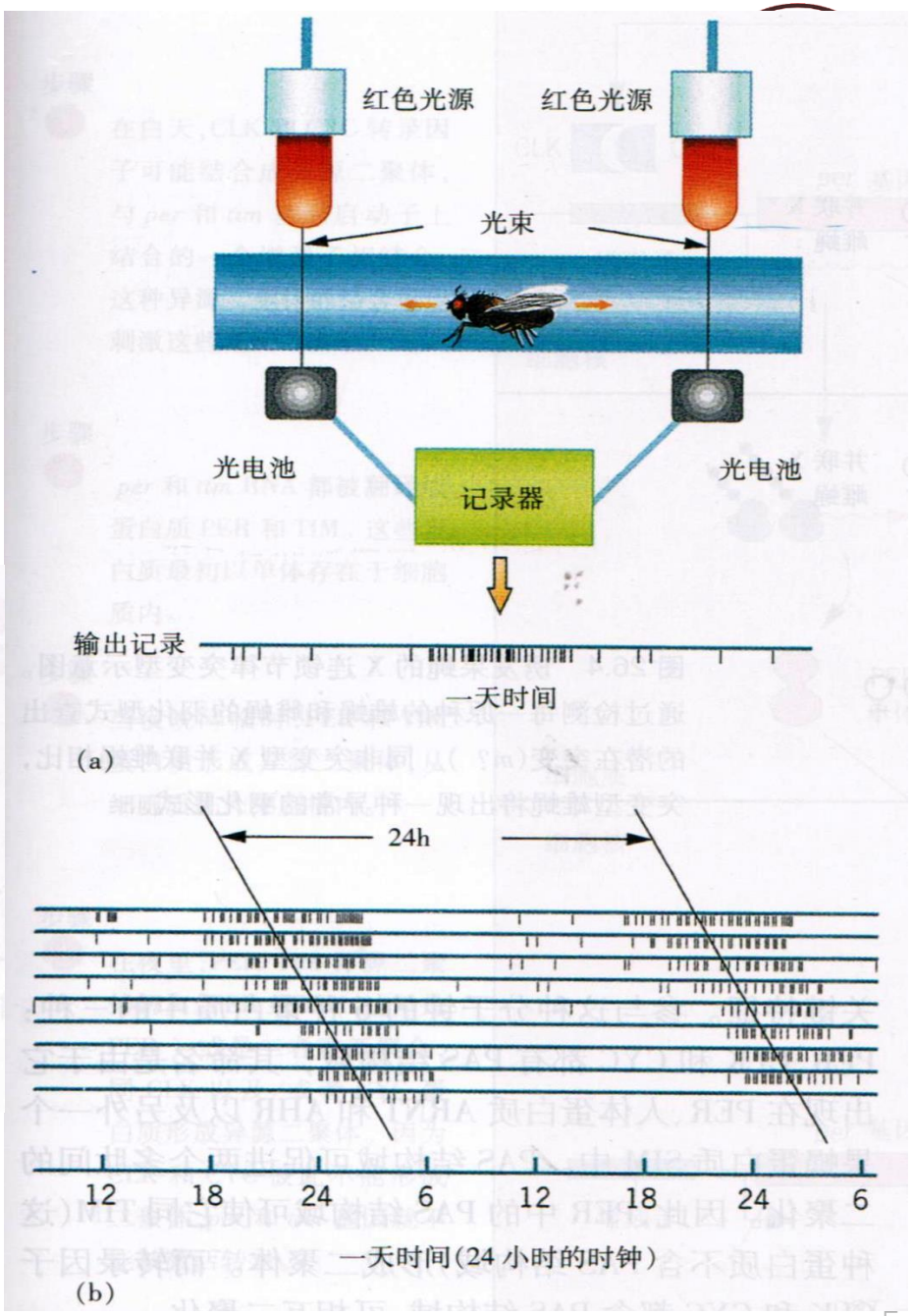

P
二倍体“卫生的”蜂后
单倍体“非卫生的”雄蜂
uu rr
×
u+ r+
F1
二倍体子代——全是“非卫生的”
uu+ rr+
F1未受精卵
单倍体雄蜂
回交产生的工蜂
洁巢行为
u r
u r+
u+ r
u+ r+
同二倍体“卫生的”打开蜂室蜂后回交
(uu rr)
uu rr
uu rr+
uu+ rr
uu+ rr+
“卫生的”
打开蜂室
除去幼虫
“非卫生的”

2、果蝇的生物学节律

果蝇的运动活性

也遵循24h周期





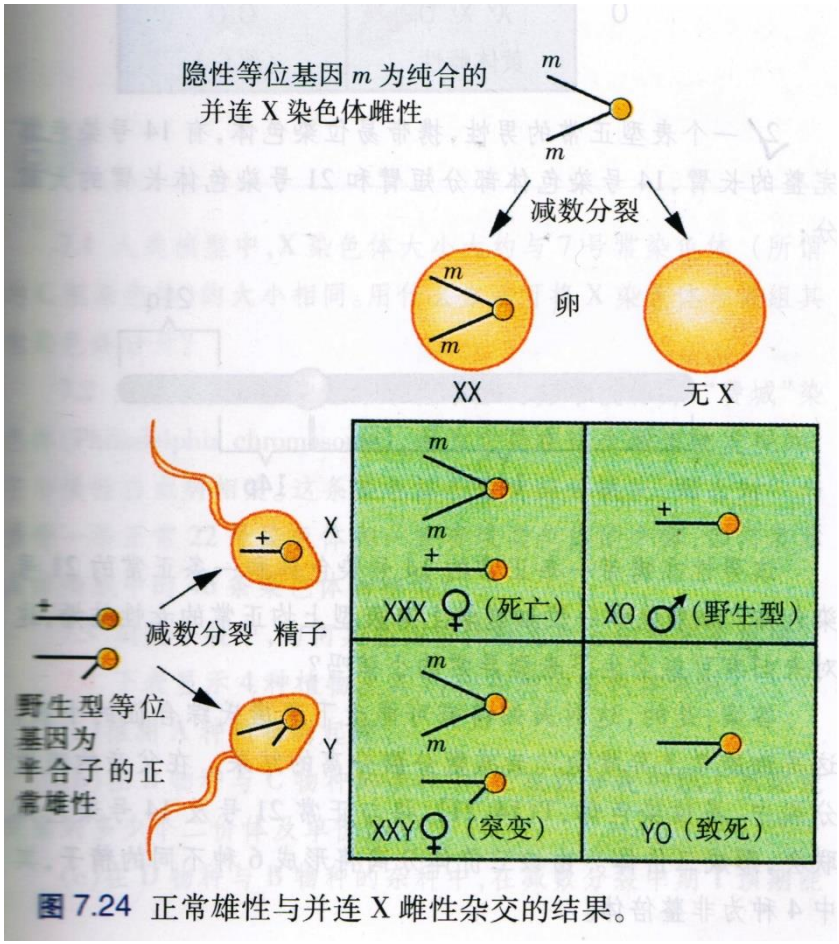
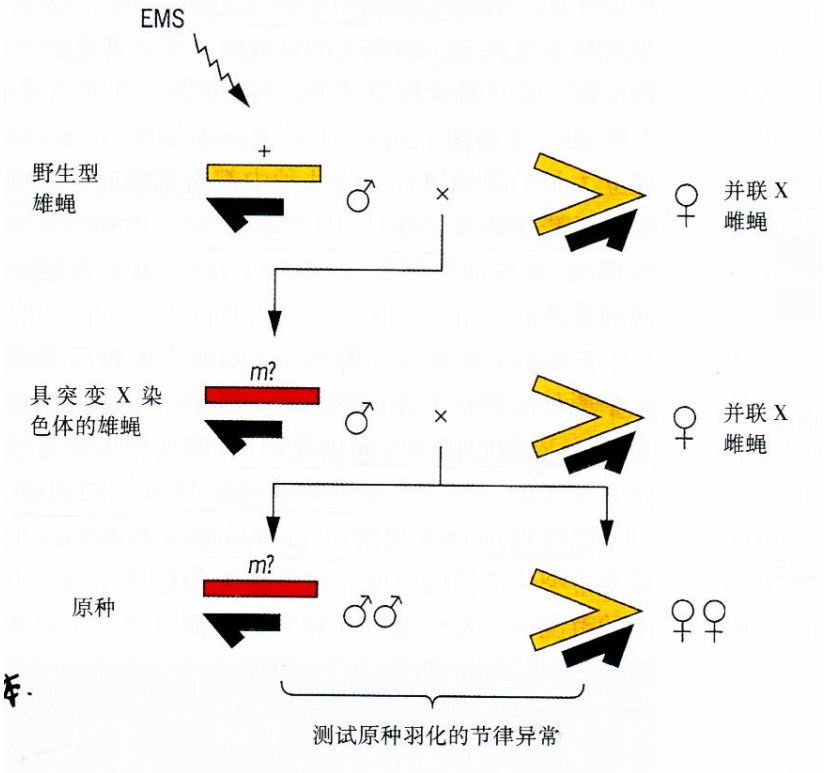
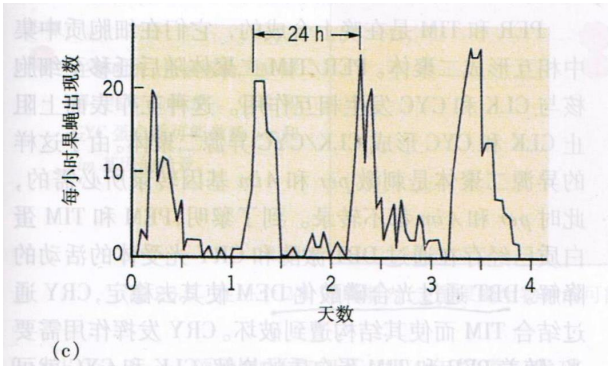
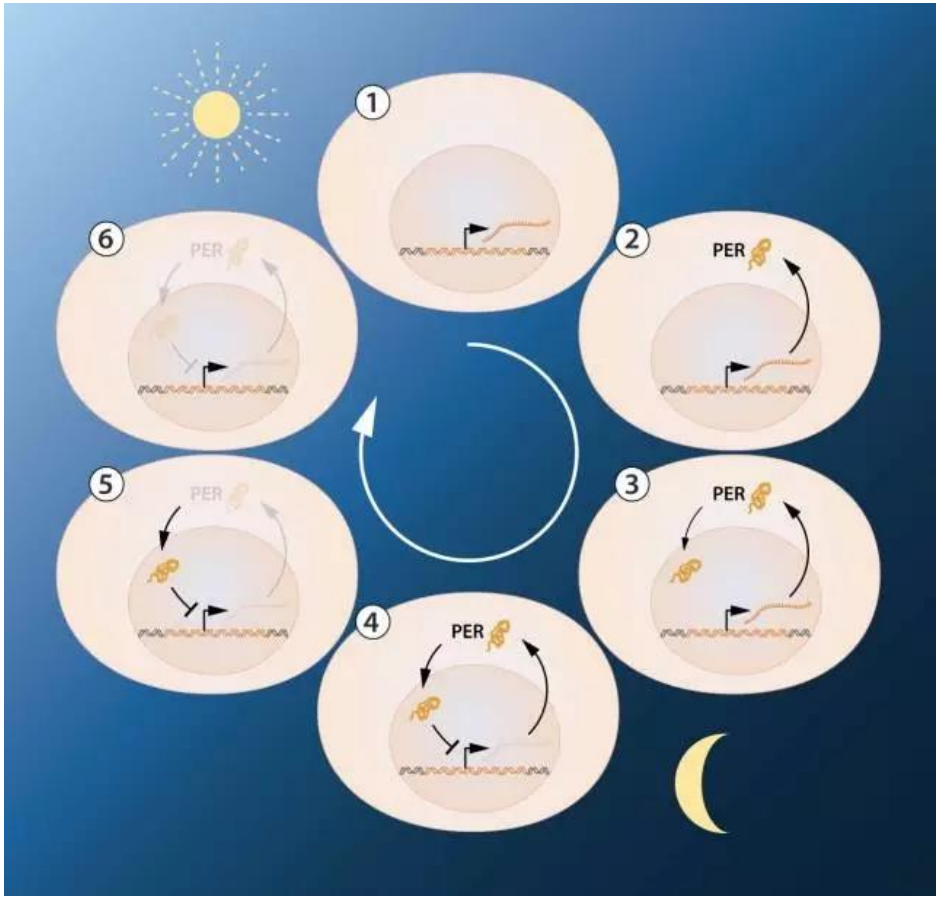


图 7.24 正常雄性与并连 X 雌性杂交的结果。





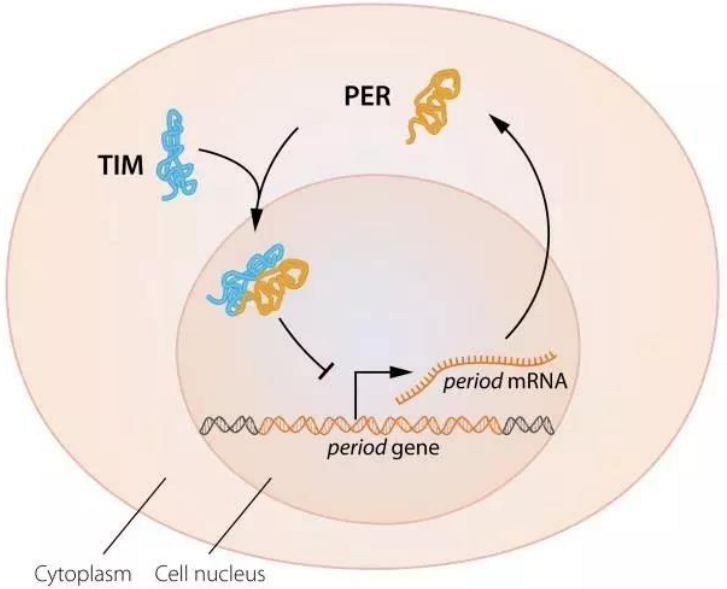


The Nobel Prize in Physiology or Medicine 2017

Jeffrey C. Hall
Prize share: 1/3

Michael Rosbash
Prize share: 1/3

Michael W. Young
Prize share: 1/3



步骤 1

在白天，CLK 和 CYC 转录因子可能结合成异源二聚体，与 *per* 和 *tim* 基因启动子上结合的一个增强子相结合。这种异源二聚体的结合可以刺激这些基因的转录。

步骤 2

per 和 *tim* RNA 都被翻译成蛋白质 PER 和 TIM。这些蛋白质最初以单体存在于细胞质内。

步骤 3

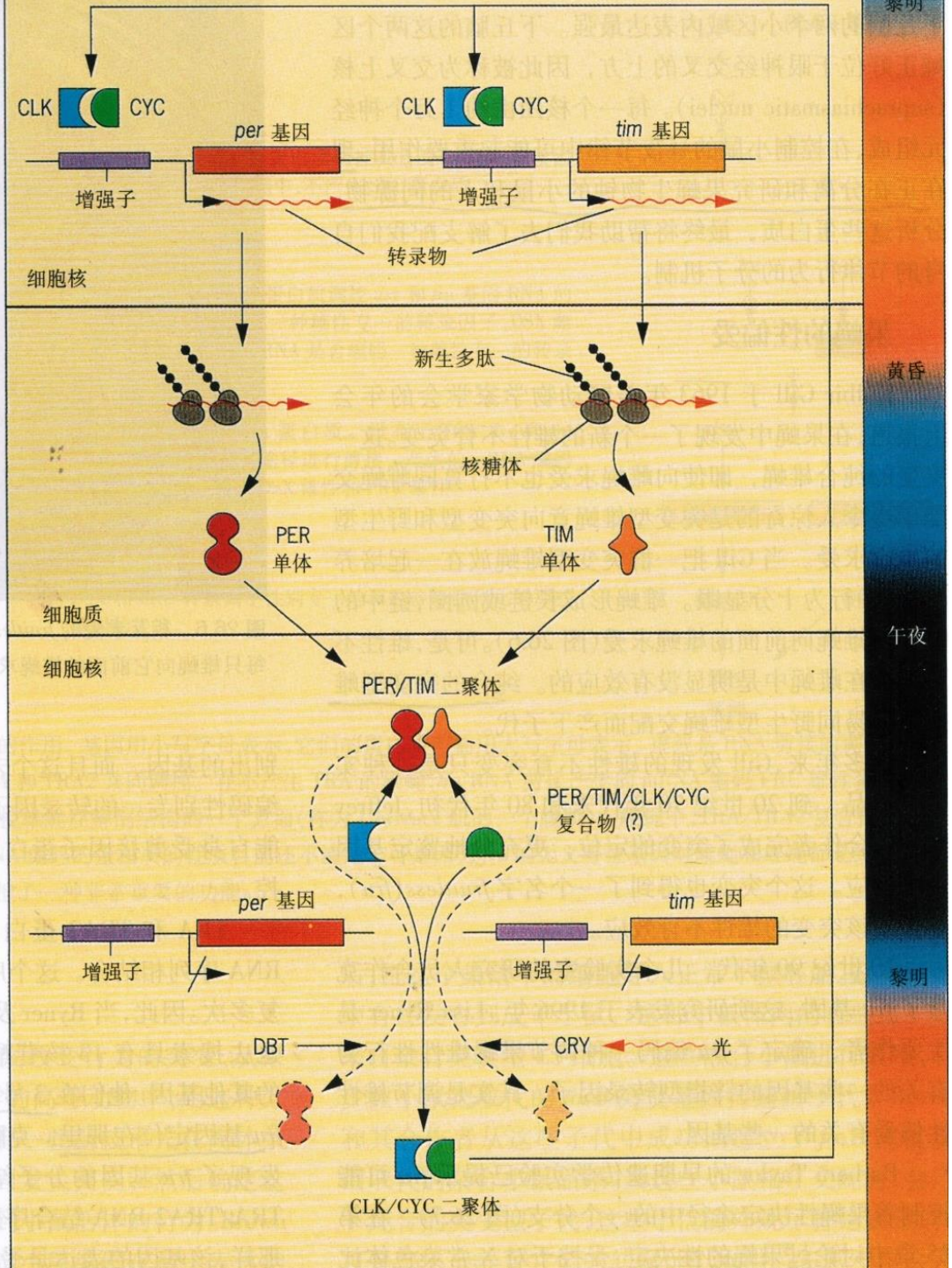
当夜晚降临时，PER 和 TIM 蛋白质形成异源二聚体，从细胞质进入细胞核内。

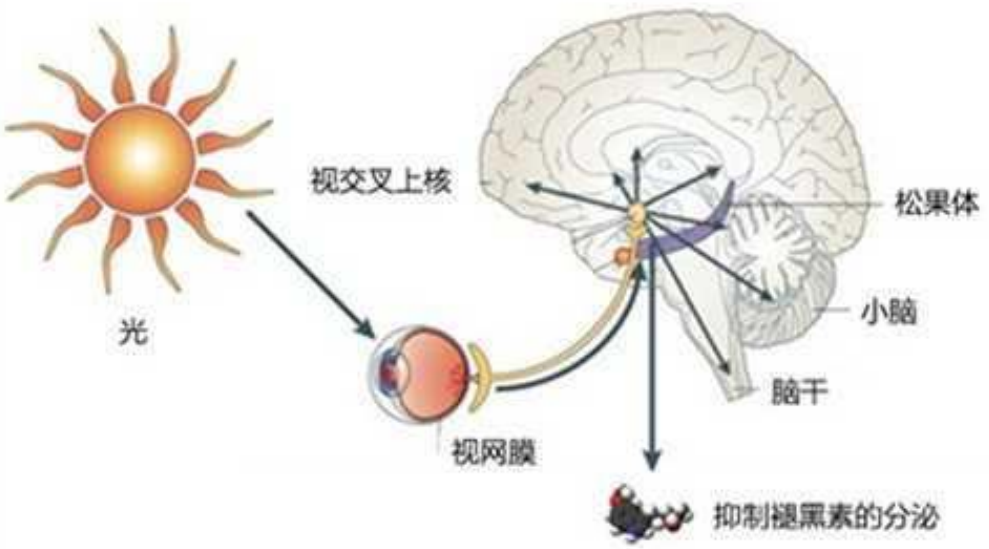
步骤 4

在夜里，PER/TIM 异源二聚体解离。PER 或 TIM（这里是 PER ）或是二者重新聚合，同 CLK 以及/或者 CYC 蛋白质形成异源二聚体。因为 CLK 和 CYC 彼此不能形成二聚体，*per* 和 *tim* 基因就不能被激活转录。

步骤 5

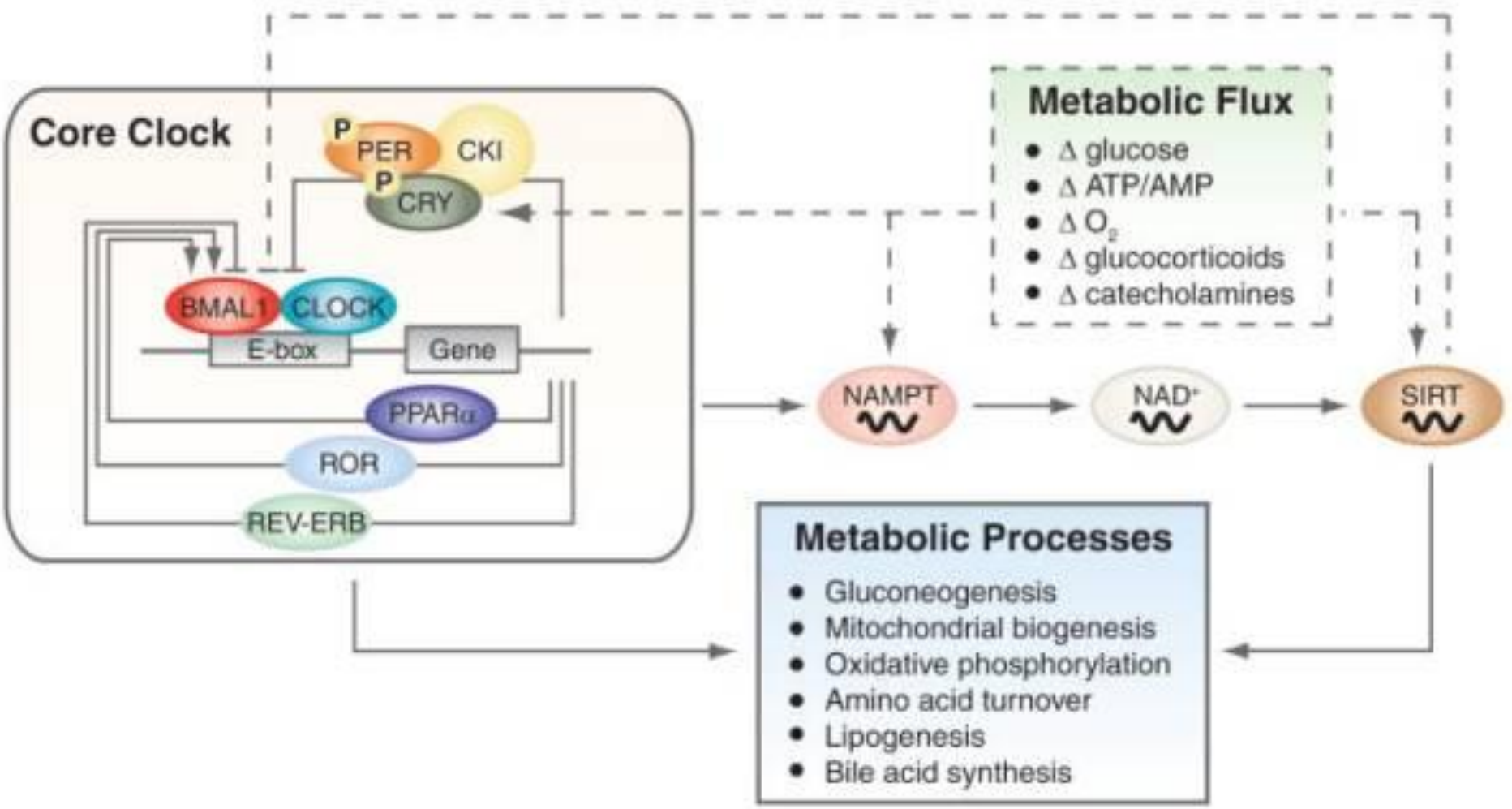
在黎明时，光敏感的 TIM 降解，PER 也降解。CLK 和 CYC 蛋白质可能激活 *per* 和 *tim* 基因的转录。




光
视交叉上核
松果体
小脑
脑干
视网膜
抑制褪黑素的分泌


高度警觉
协调性最强
反应最快
血压上升速度最快
体温最高
皮质醇释放
血压最高
体温最低
褪黑素分泌
深度睡眠
12
6
18
24

哺乳动物细胞中，约有 10%的基因会呈现昼夜振荡表达的模式



想要健康不胖?

---- 睡好、少吃，管好生物钟!

① 生物钟基因突变的小鼠表现出肥胖、代谢综合征、睡眠减少、进食时间改变；同样食用高脂饮食，进食时间异常的小鼠比进食时间正常的小鼠体重增加更多；

② 昼夜节律紊乱的人超重及糖尿病风险更高；

③ 睡眠不足对糖耐受及体重有不利影响，并增加饥饿感，恢复睡眠时间可逆转上述症状；

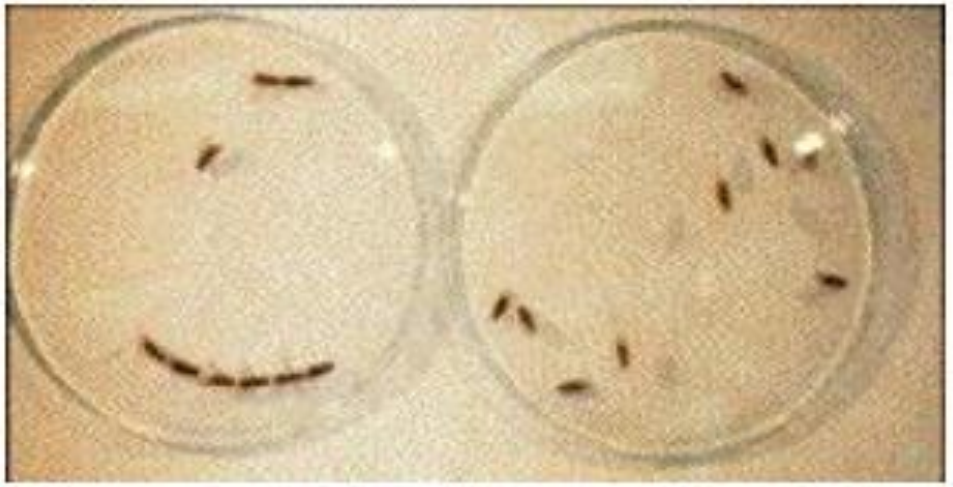
④ 人体试验发现，恢复正常进食时间可帮助减重并改善睡眠质量。

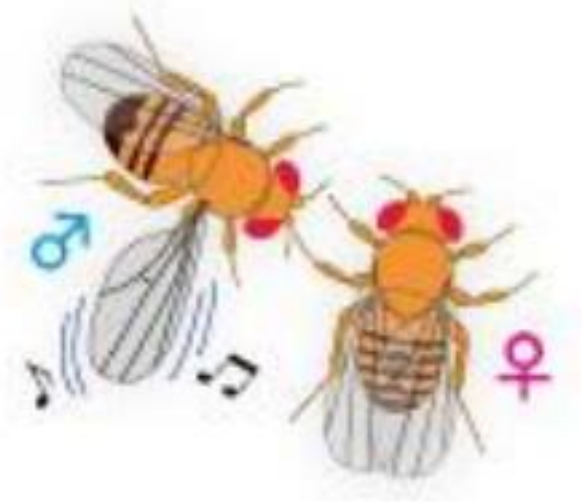
⑤ 改善睡眠及限时进食在动物实验及初步人类研究中展现出重置生物钟并恢复健康代谢的潜能；

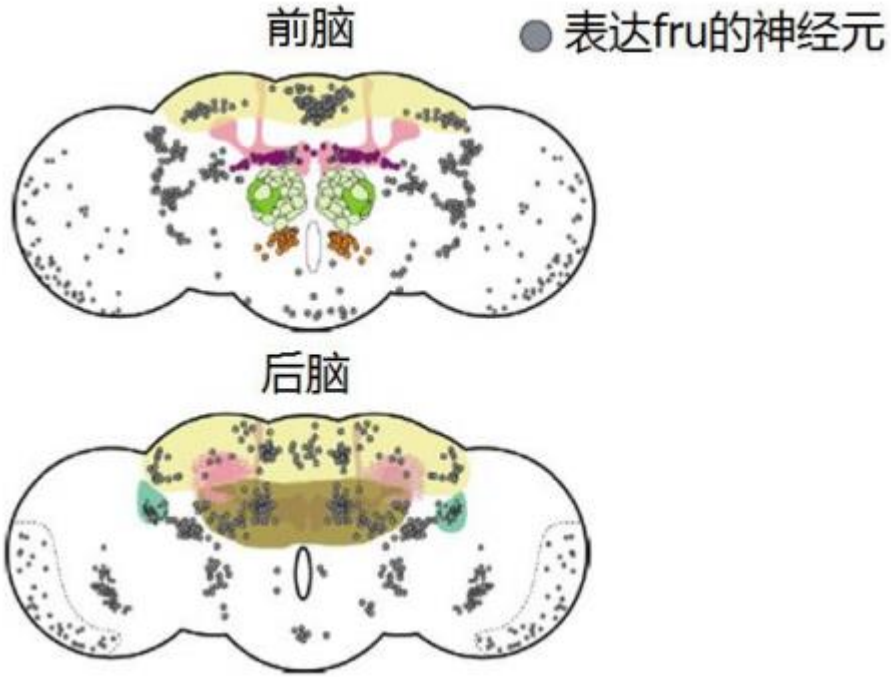
Resetting the Circadian Clock Might Boost Metabolic Health. (JAMA. 2017)

3. 果蝇的行为分析

果蝇fru突变与求偶行为







Nature 2005, 438(7065):229

4. 小鼠行为的遗传学分析

1）雌鼠的养育能力

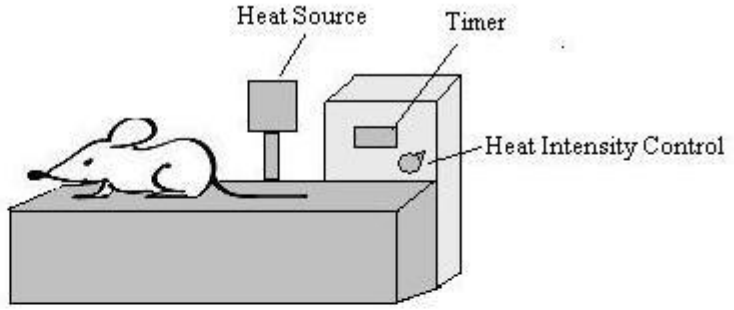
雌鼠天生表现对幼鼠的哺乳、关怀。鼠 fosB基因剔除，不再表现母性行为。

D

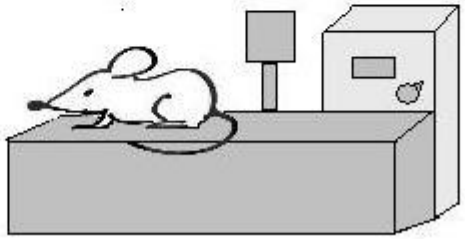
Mouse Behavior Test

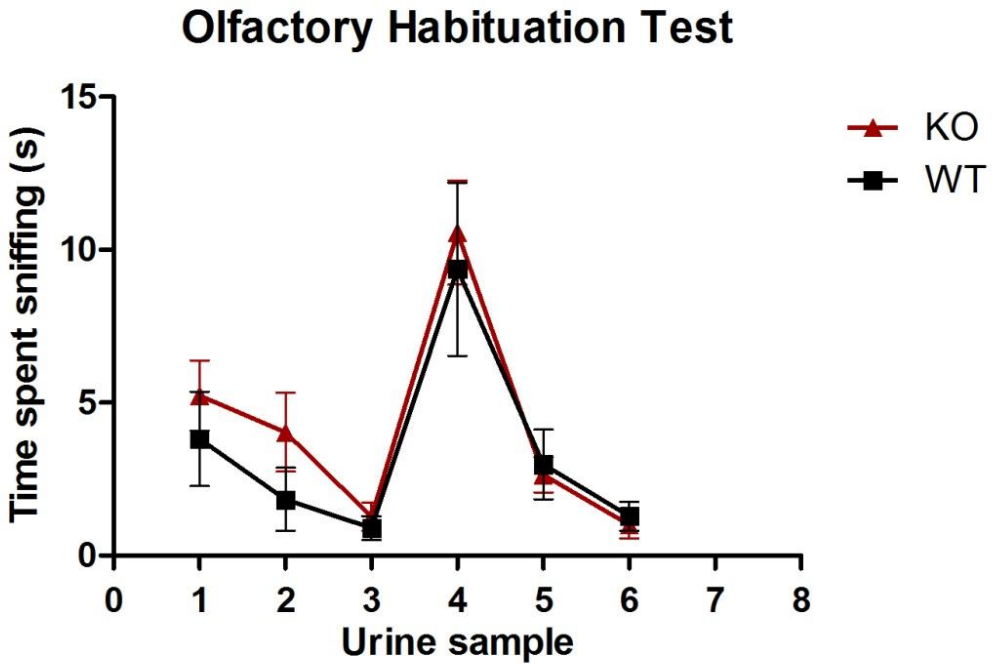
- Pain： Tail flick; Hot-plate;
- Olfactory: Olfactory habituation
- Learning and Memory： Morris water maze
- Anxiety： Open field； Elevated plus maze;
- Depression： Forced swimming; Tail suspension
- Social ability: New obstacle reconigition
- ……

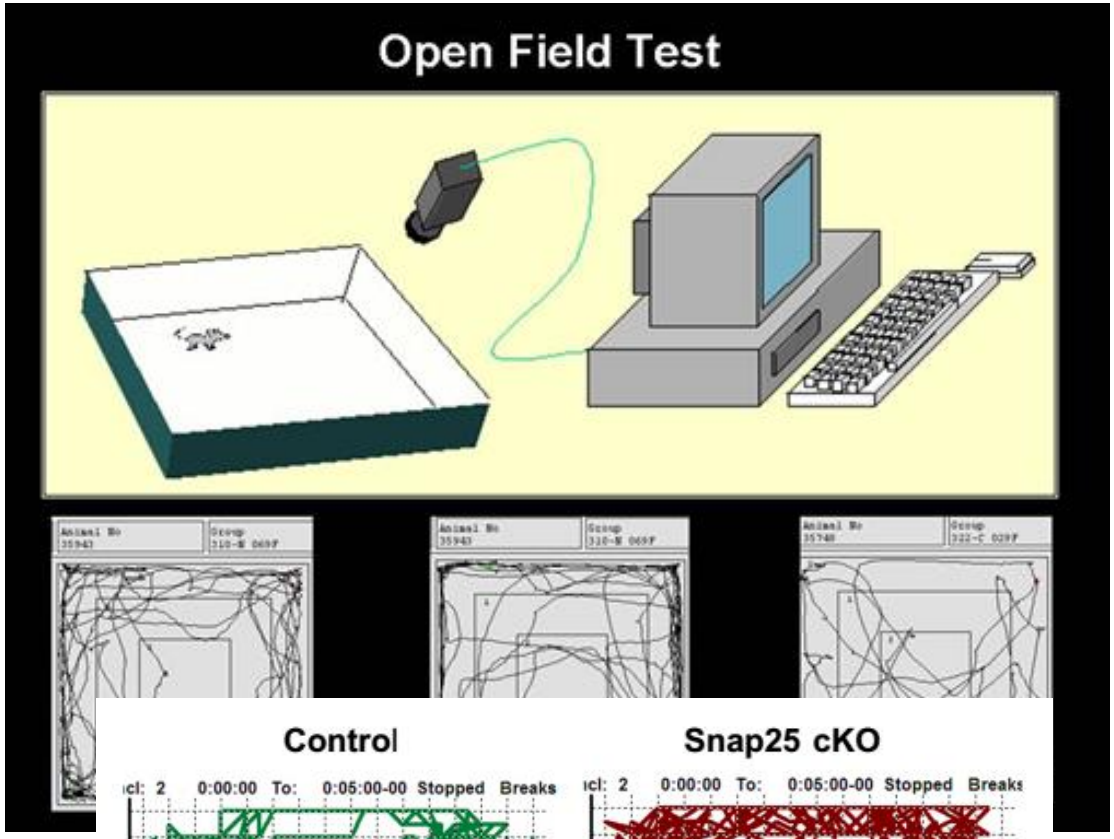
Before Tail Flick

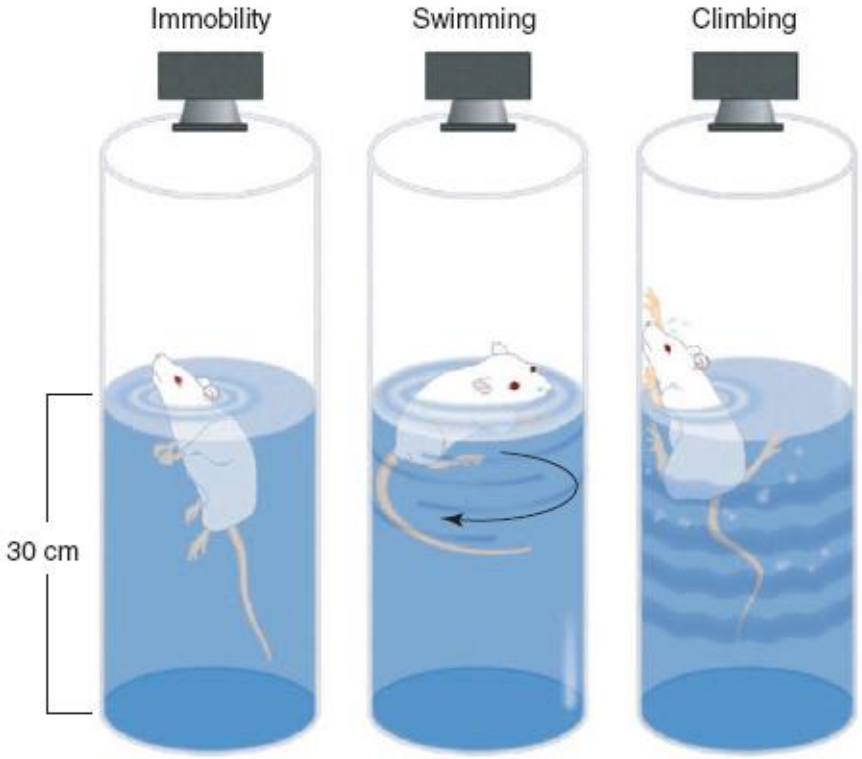


After Tail Flick

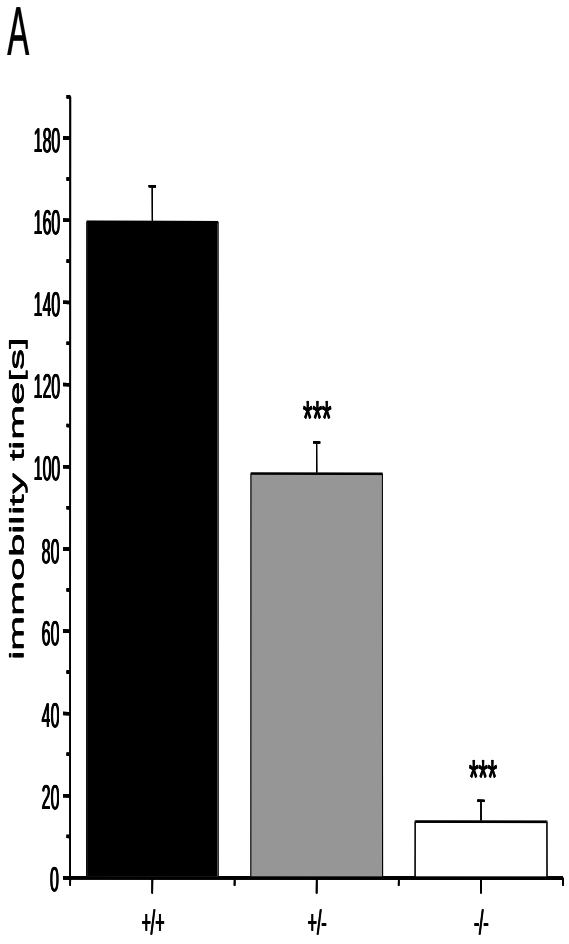


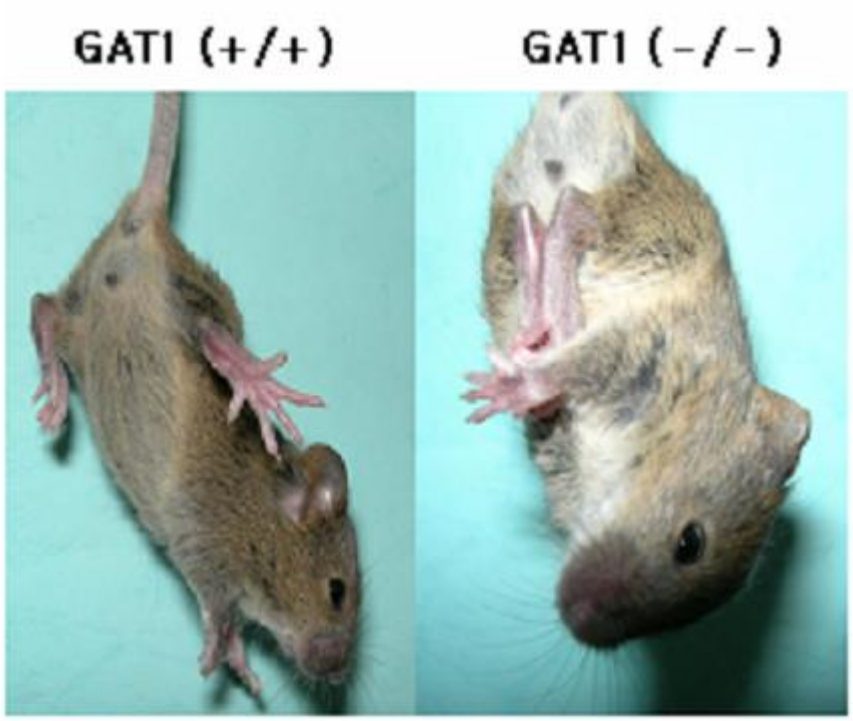

Olfactory Habituation Test
Time spent sniffing (s)
15
10
5
0
0
1
2
3
4
5
6
7
8
Urine sample
KO
WT


Open Field Test
Control
Snap25 cKO
0:00:00 To: 0:05:00-00 Stopped Breaks
0:00:00 To: 0:05:00-00 Stopped Breaks

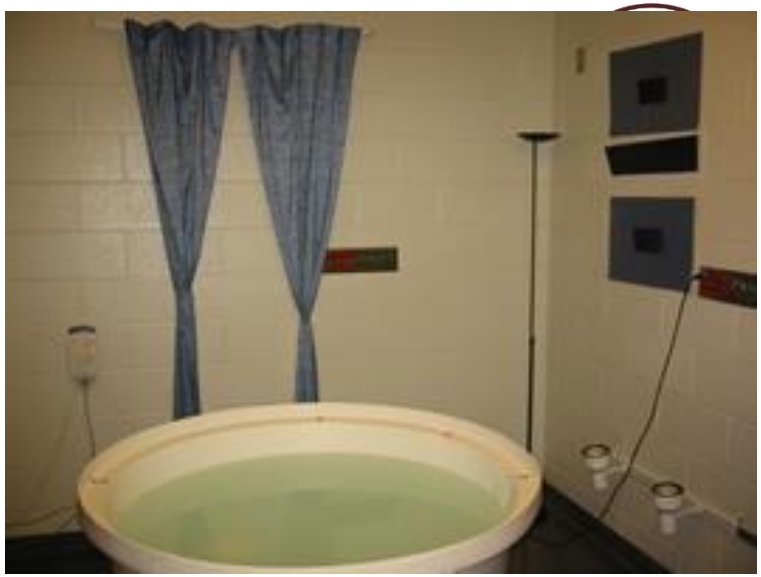


实验模型	评价指标	抑郁趋向
1. 小鼠强迫游泳实验 (FST)	水中不动时间	↑

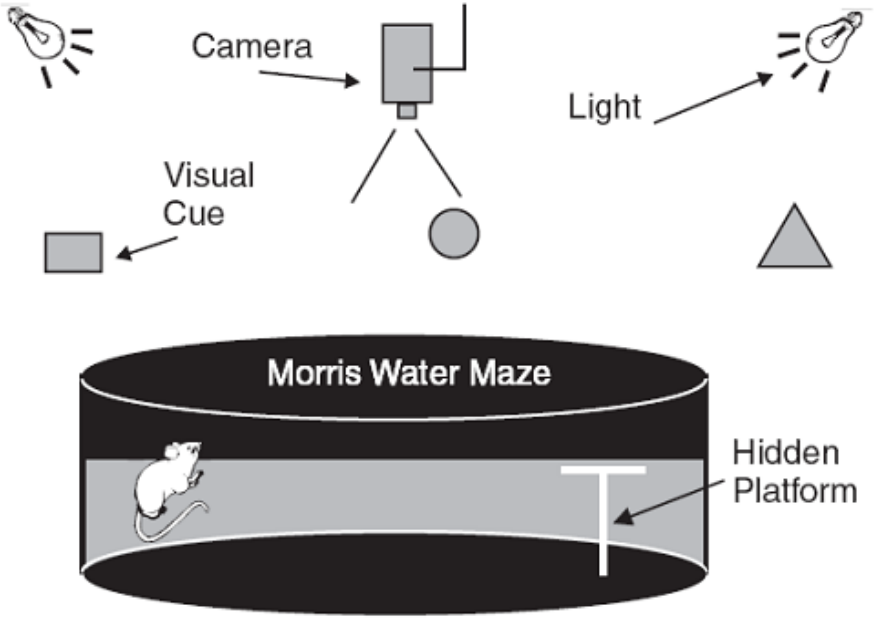



GAT1 (+/+)
GAT1 (-/-)

Morris水迷宫：

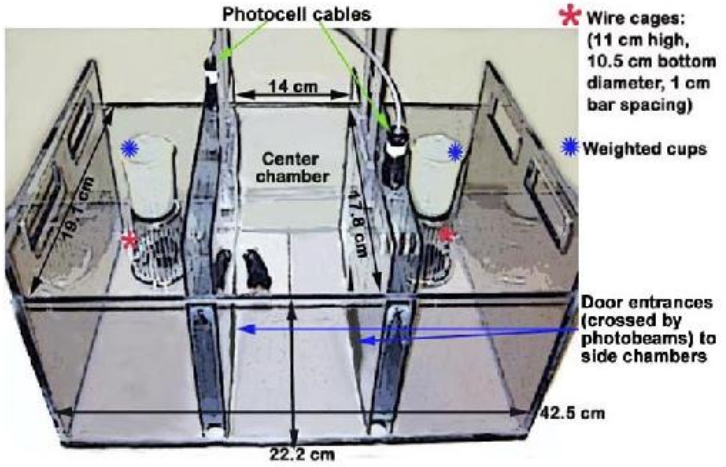


测试实验动物对空间位置觉和方向觉（空间定位）的学习记忆能力。

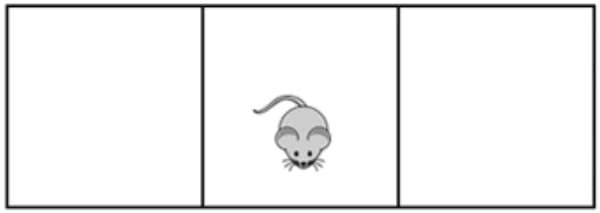


社交能力测试：

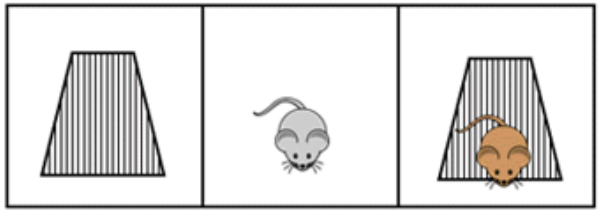
测试动物的社交能力、好奇心



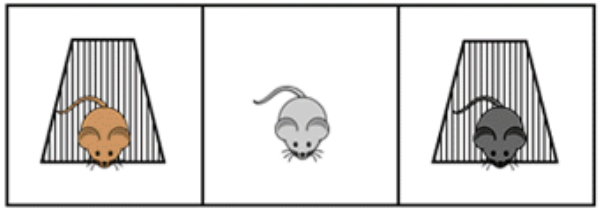
Adapted from Moy *et. al.*, 2007. *Behavioral Brain Research* 176(1):4-20.



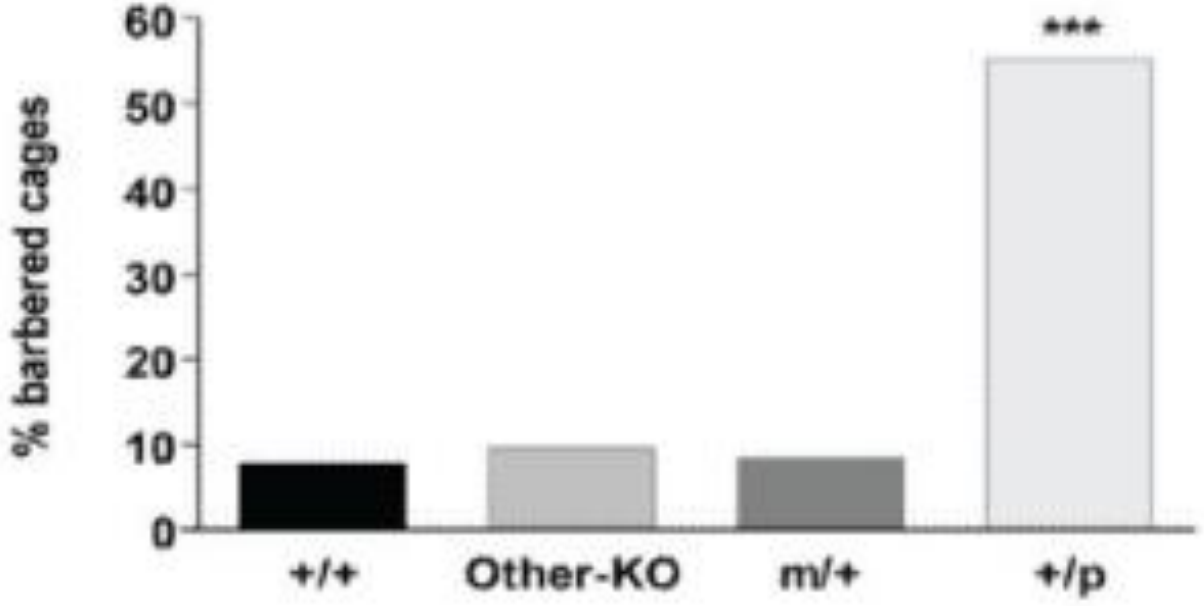
Habituation: Empty Apparatus

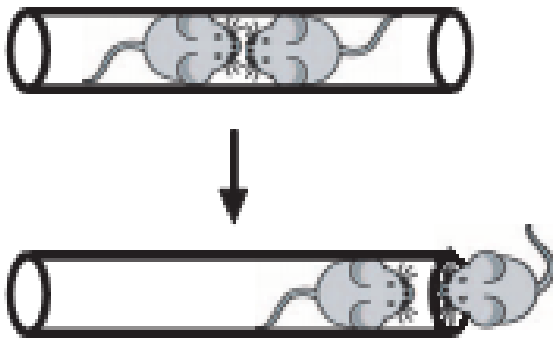


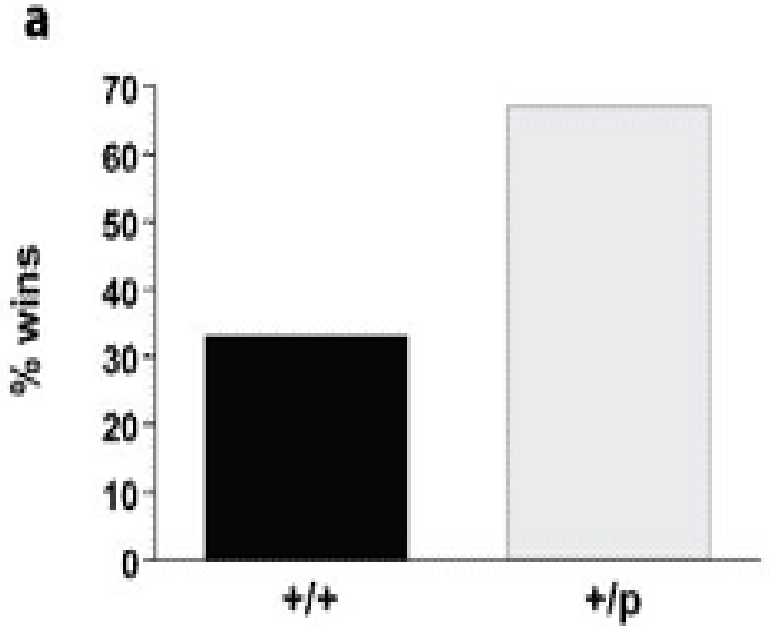
Sociability: Novel Object; Mouse 1

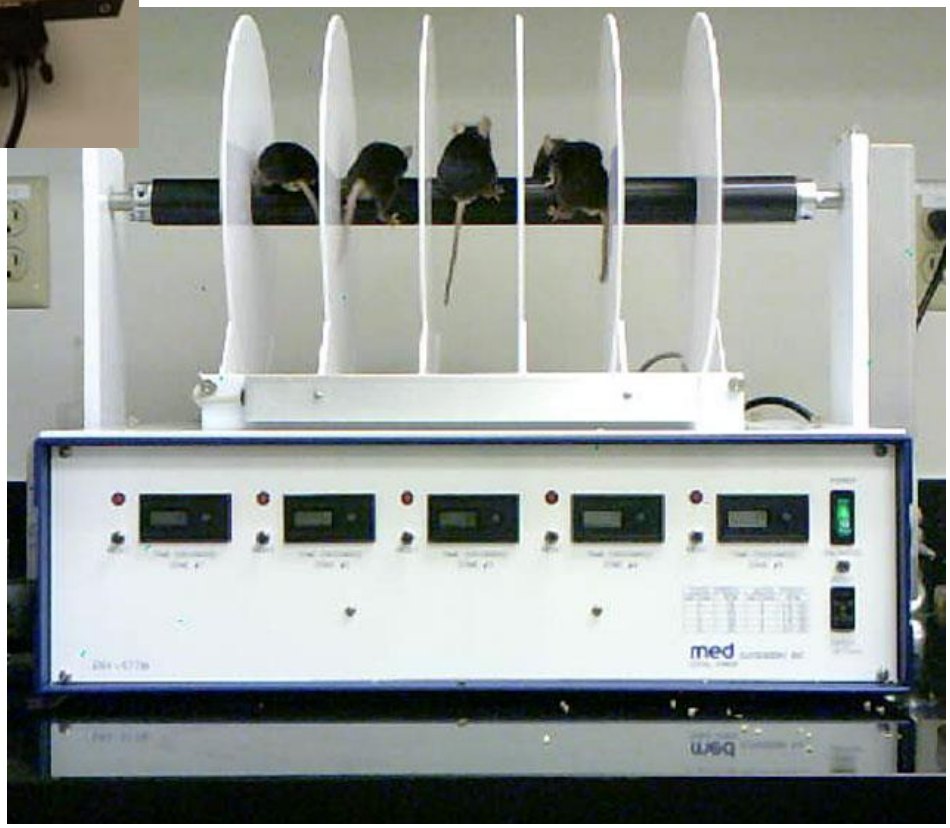


Social Novelty: Mouse 1; Mouse 2


% barbered cages
60
50
40
30
20
10
0
***
+/+
Other-KO
m/+
+/p




a
% wins
70
60
50
40
30
20
10
0
+/+
+/p


med

Gait Analysis

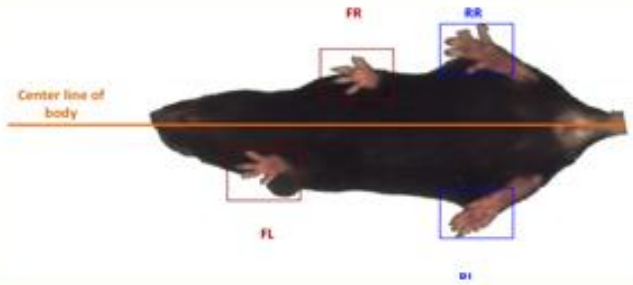
Normal

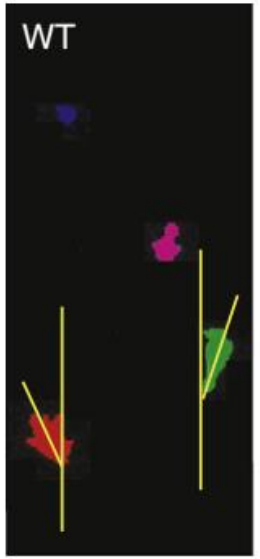
Severe Ataxia

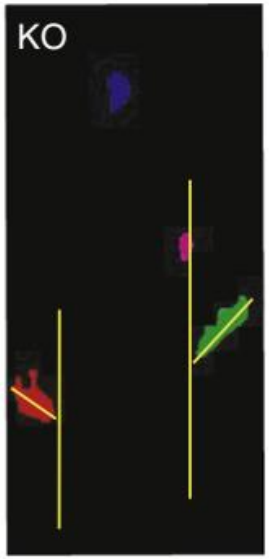
Foot drag

Mis-Step (foot placement)

Variable Stride Length







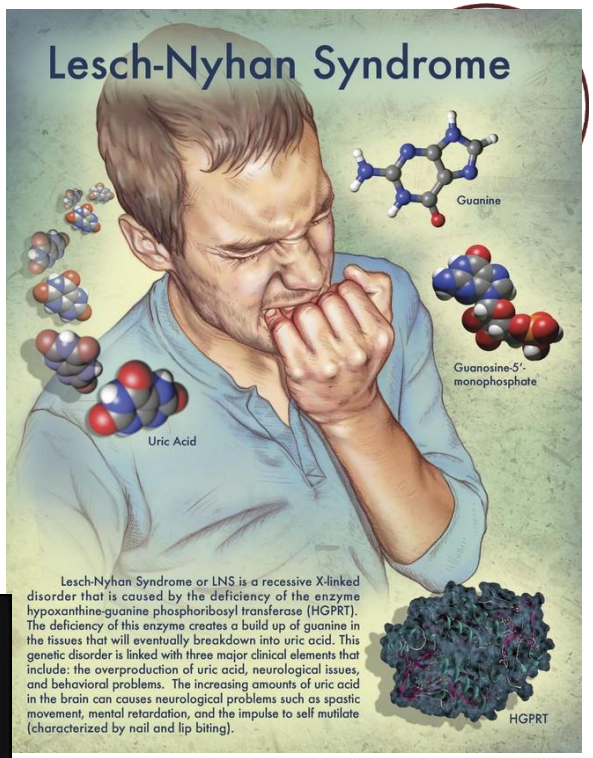
https://www.jove.com/

二、遗传变异对人类行为的影响

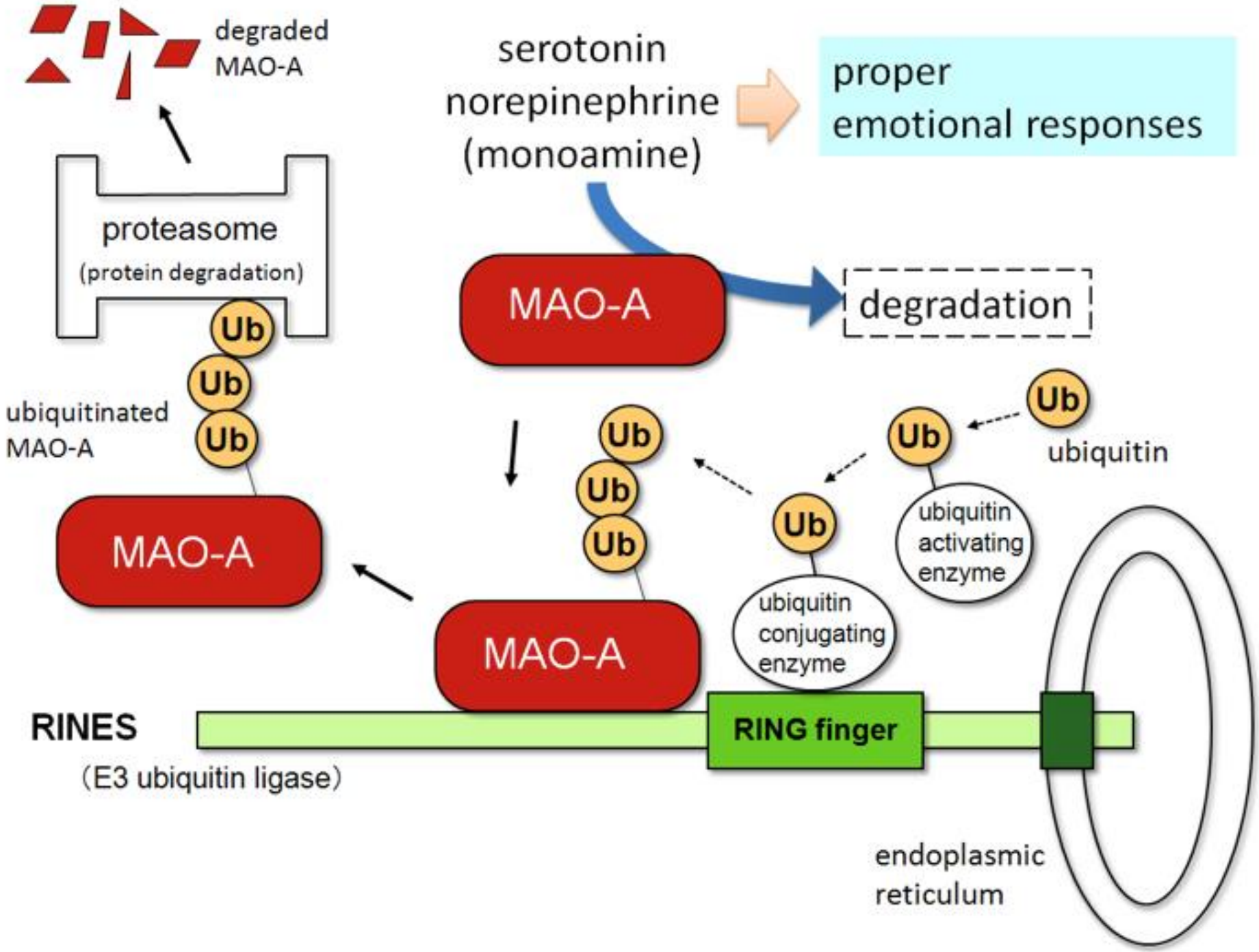
1. 多种染色体病患者具有智力迟滞表现

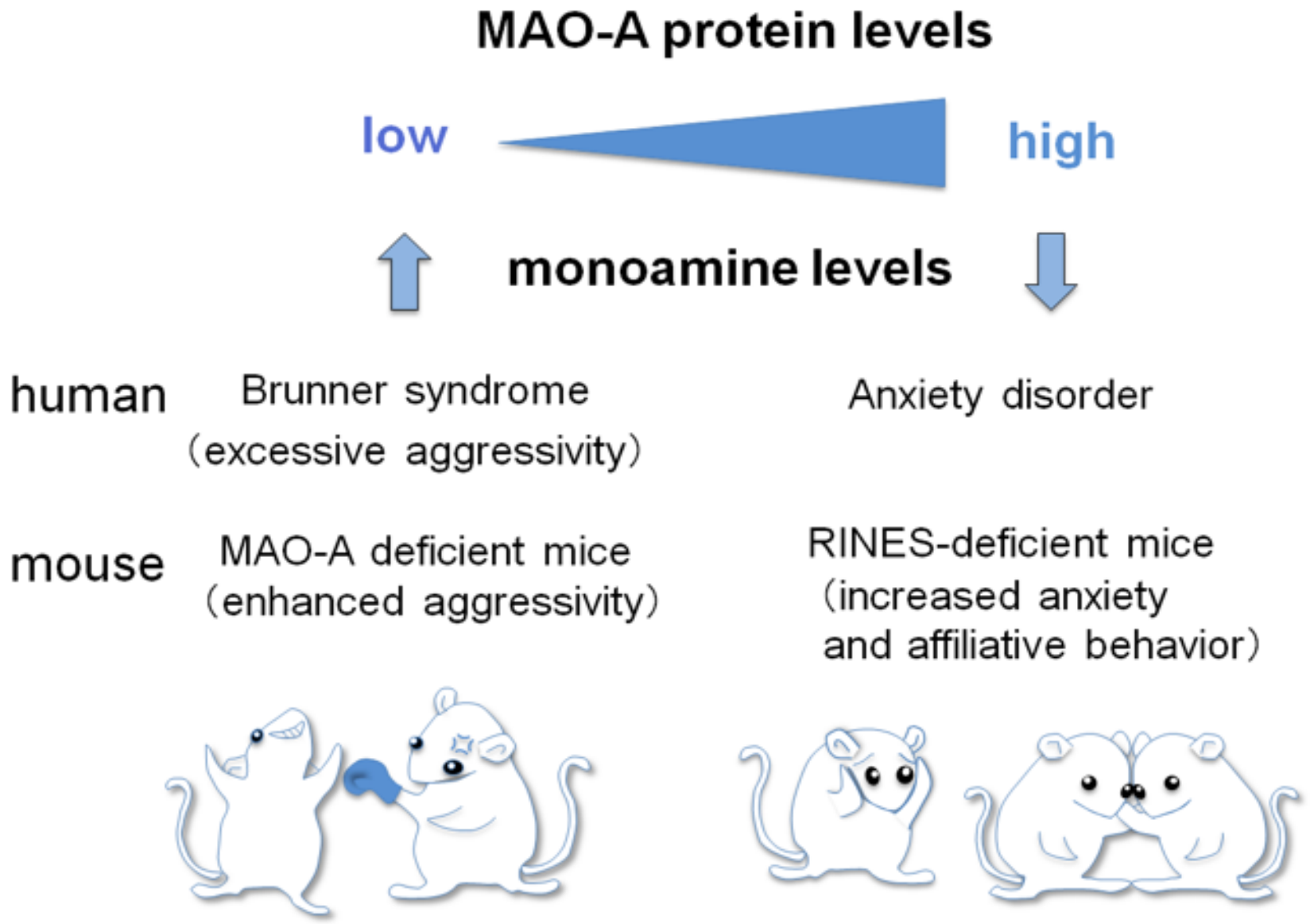
2. 单基因突变与人类行为

A new study from Nancy Wexler, in Venezuela in the 1990s with a boy with Huntington's disease, suggests there may be ways to delay the onset of the disease.



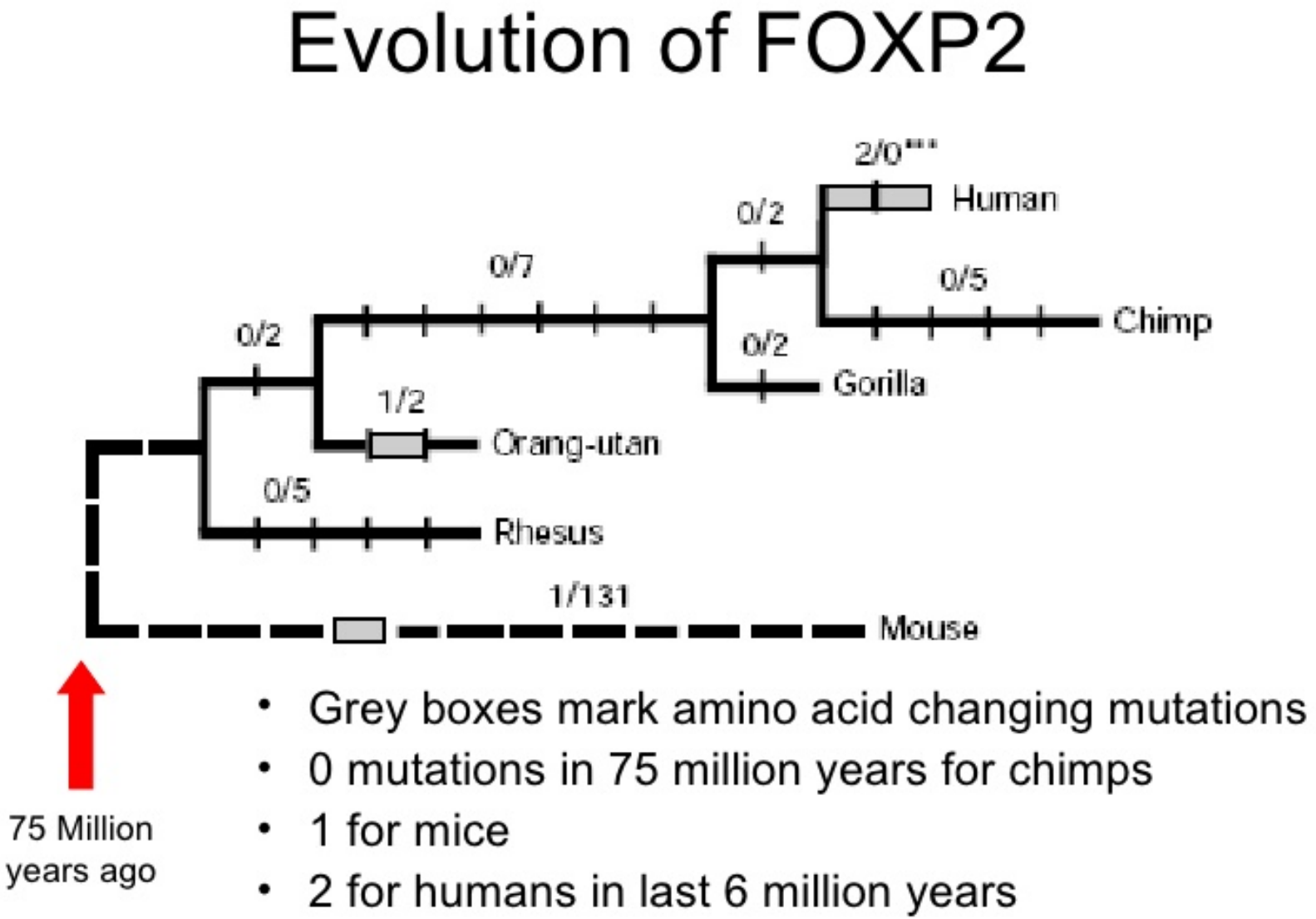
- MAOA: enzyme that degrades/metabolizes amine neurotransmitters (dopamine [DA] , noradrenalin[NE], serotonin[5-HT])
- Rare genetic disorder: an*MAOA* mutation leads to *MAOA* deficiency and an excess of monoamine transmitters=excessive impulsive behavior (hypersexuality, sleep disorder, extreme mood swings, tendency to violence)-Brunner syndrome.
- X Chromosome (Xp11.23-11.4)
  - Null allele at MAOA locus-male antisocial behavior in Dutch kindred


degraded
MAO-A
serotonin
norepinephrine
(monoamine)
proper
emotional responses
proteasome
(protein degradation)
MAO-A
degradation
Ub
Ub
Ub
ubiquitinated
MAO-A
Ub
ubiquitin
Ub
ubiquitin
activating
enzyme
Ub
ubiquitin
conjugating
enzyme
MAO-A
MAO-A
RINES
(E3 ubiquitin ligase)
RING finger
endoplasmic
reticulum

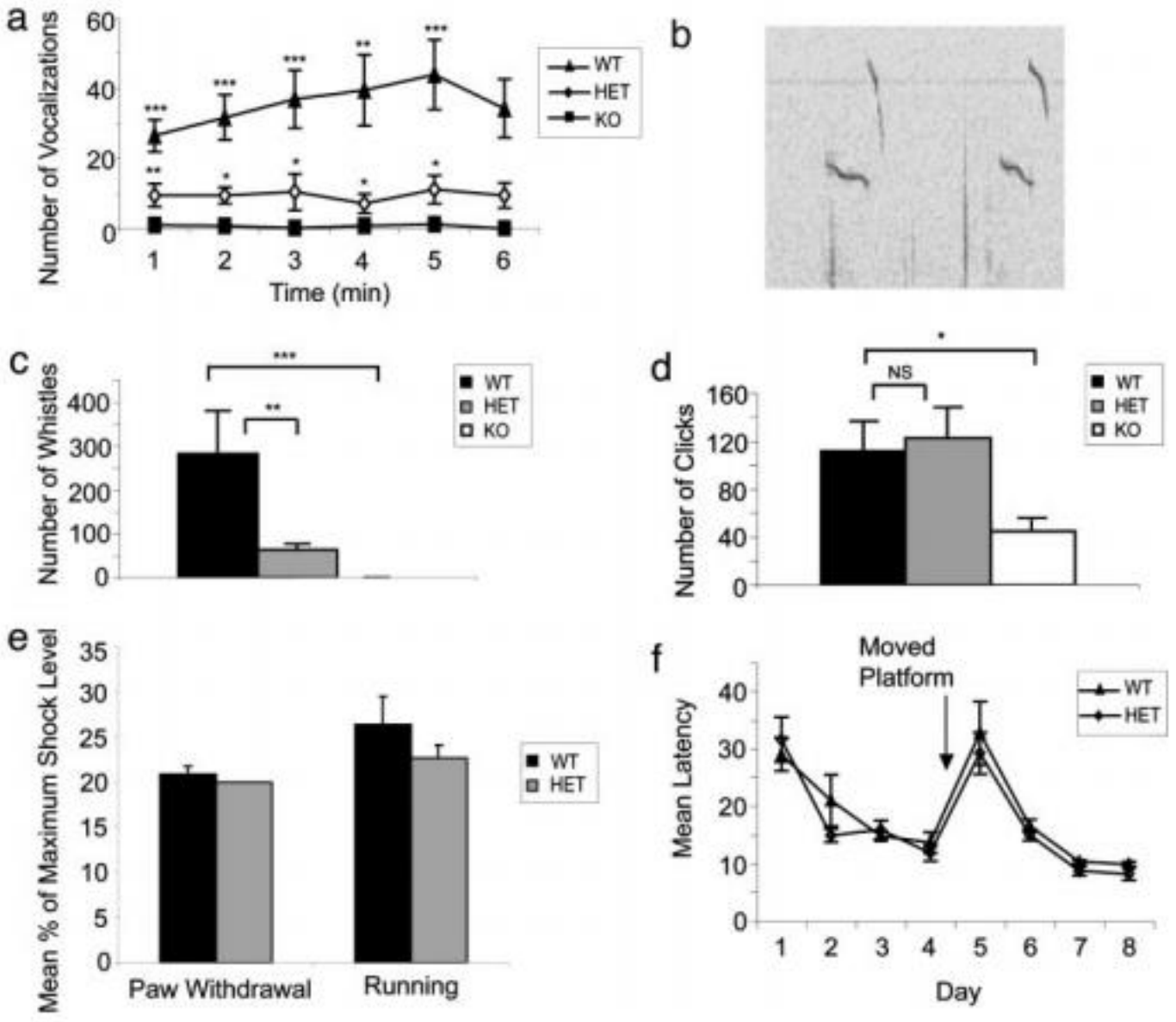


"Rines E3 Ubiquitin Ligase Regulates MAO-A Levels and Emotional Responses." The Journal of Neuroscience, 2013. doi:10.1523

决定人类语言功能关键基因



Molecular evolution of FOXP2, a gene involved in speech and language



Altered ultrasonic vocalization in mice with a disruption in the Foxp2 gene. *PNAS, 2005*

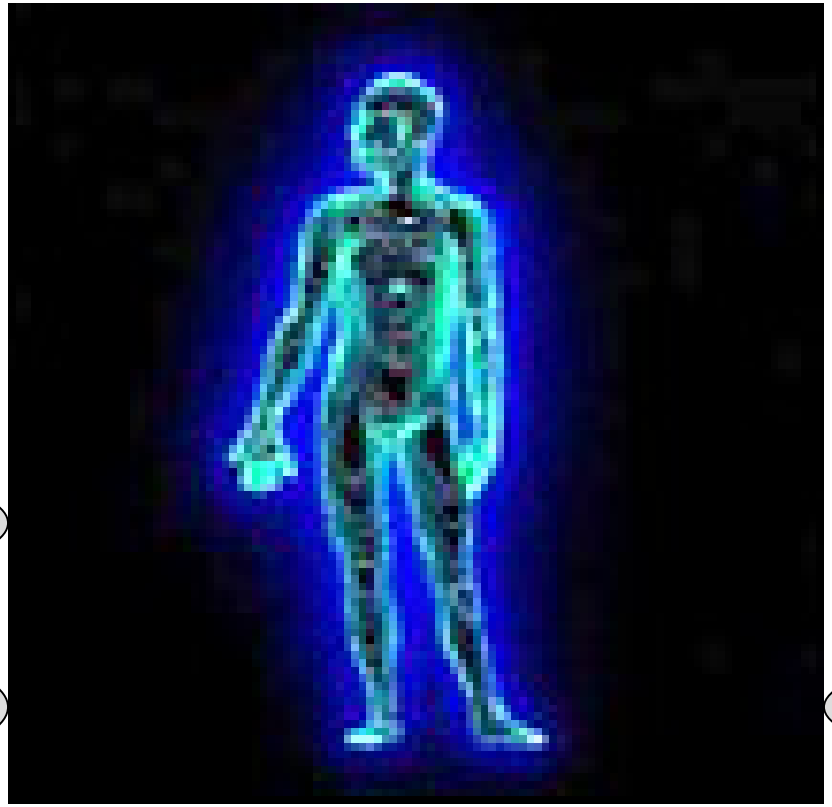
3. 复杂的人类行为

diabetes

obesity

hypertension

schizophrenia

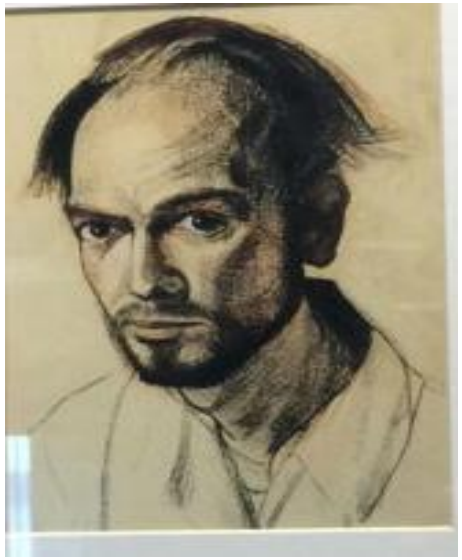


cleft palate

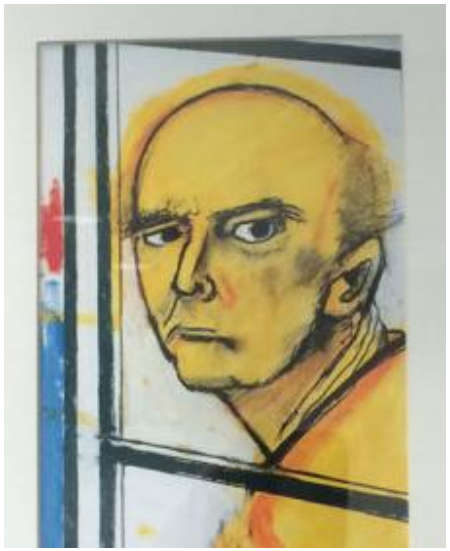
intelligence

neural tube defects

most common diseases



William Utermohlen
（1933-2007）



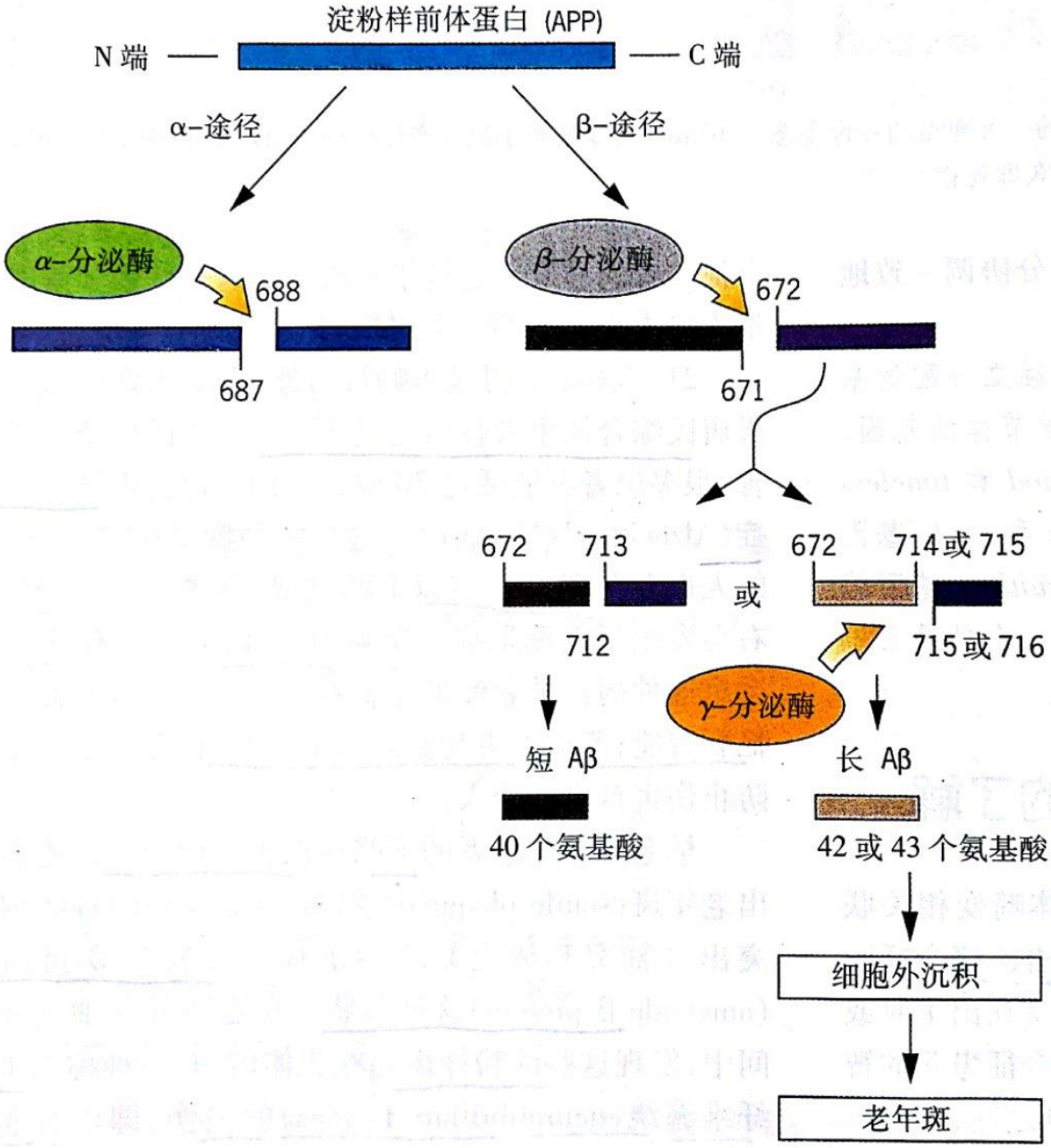
1996

1997

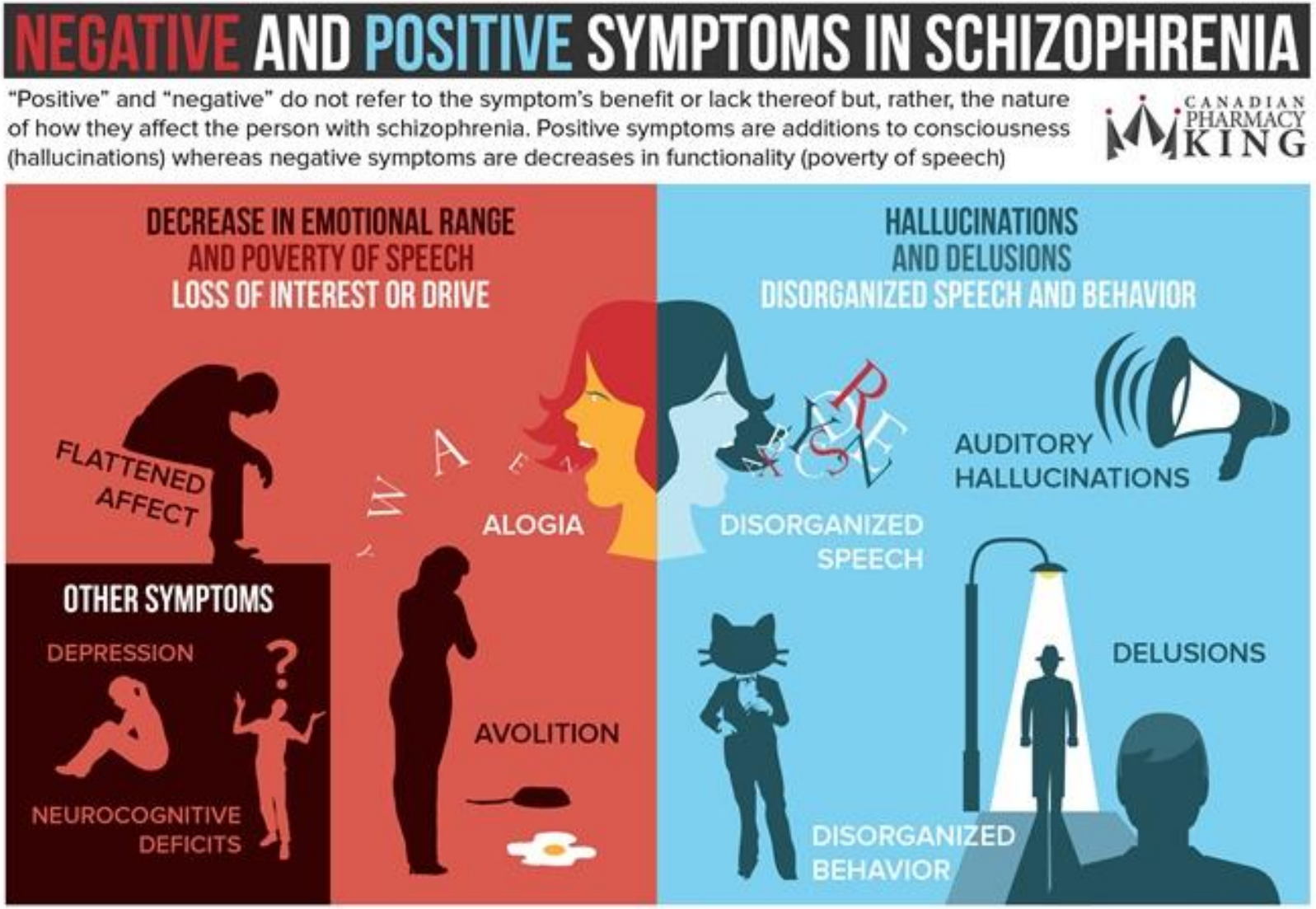
1998

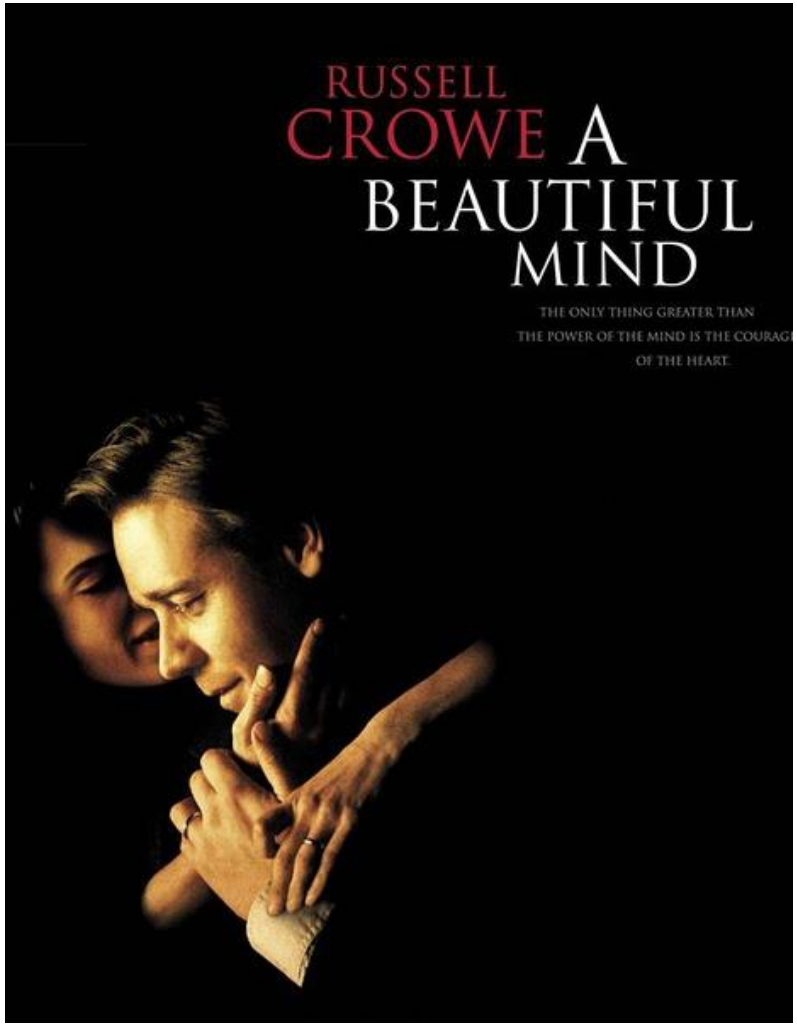
1999

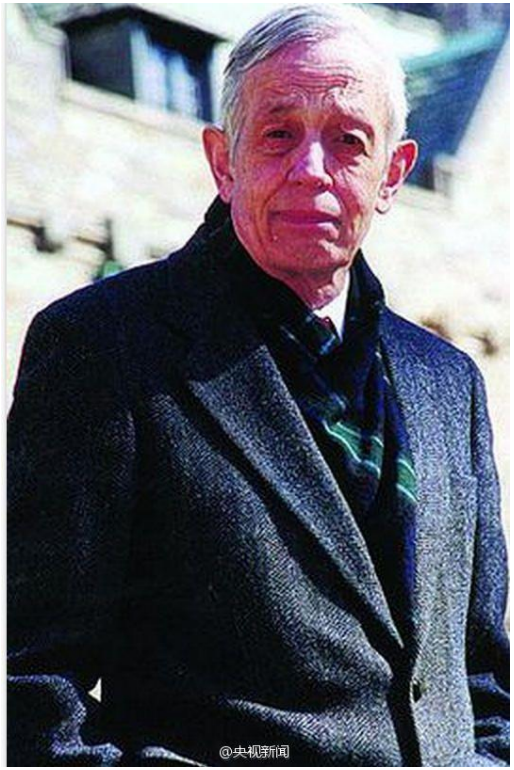
2000


淀粉样前体蛋白 (APP)
N 端
C 端
α-途径
β-途径
α-分泌酶
688
687
β-分泌酶
672
671
672
713
712
或
672
714或715
715或716
γ-分泌酶
短 Aβ
40 个氨基酸
长 Aβ
42 或 43 个氨基酸
细胞外沉积
老年斑

精神分裂症：多基因决定


NEGATIVE AND POSITIVE SYMPTOMS IN SCHIZOPHRENIA
"Positive" and "negative" do not refer to the symptom's benefit or lack thereof but, rather, the nature of how they affect the person with schizophrenia. Positive symptoms are additions to consciousness (hallucinations) whereas negative symptoms are decreases in functionality (poverty of speech)
CANADIAN PHARMACY KING
DECREASE IN EMOTIONAL RANGE
AND POVERTY OF SPEECH
LOSS OF INTEREST OR DRIVE
FLATTENED AFFECT
ALOGIA
AVOLITION
OTHER SYMPTOMS
DEPRESSION
NEUROCOGNITIVE DEFICITS
HALLUCINATIONS
AND DELUSIONS
DISORGANIZED SPEECH AND BEHAVIOR
AUDITORY HALLUCINATIONS
DISORGANIZED SPEECH
DELUSIONS
DISORGANIZED BEHAVIOR





John Nash（1928—2015），著名数学家、经济学家，1994年度诺贝尔经济学奖的获得者，曾患有长达30年的精神分裂