ECNP Summer School – 28 June 2016

How pharmaceutical companies develop new drugs

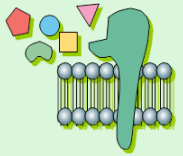
Gerry Dawson

P1vital LTD.

Overview

Introduction

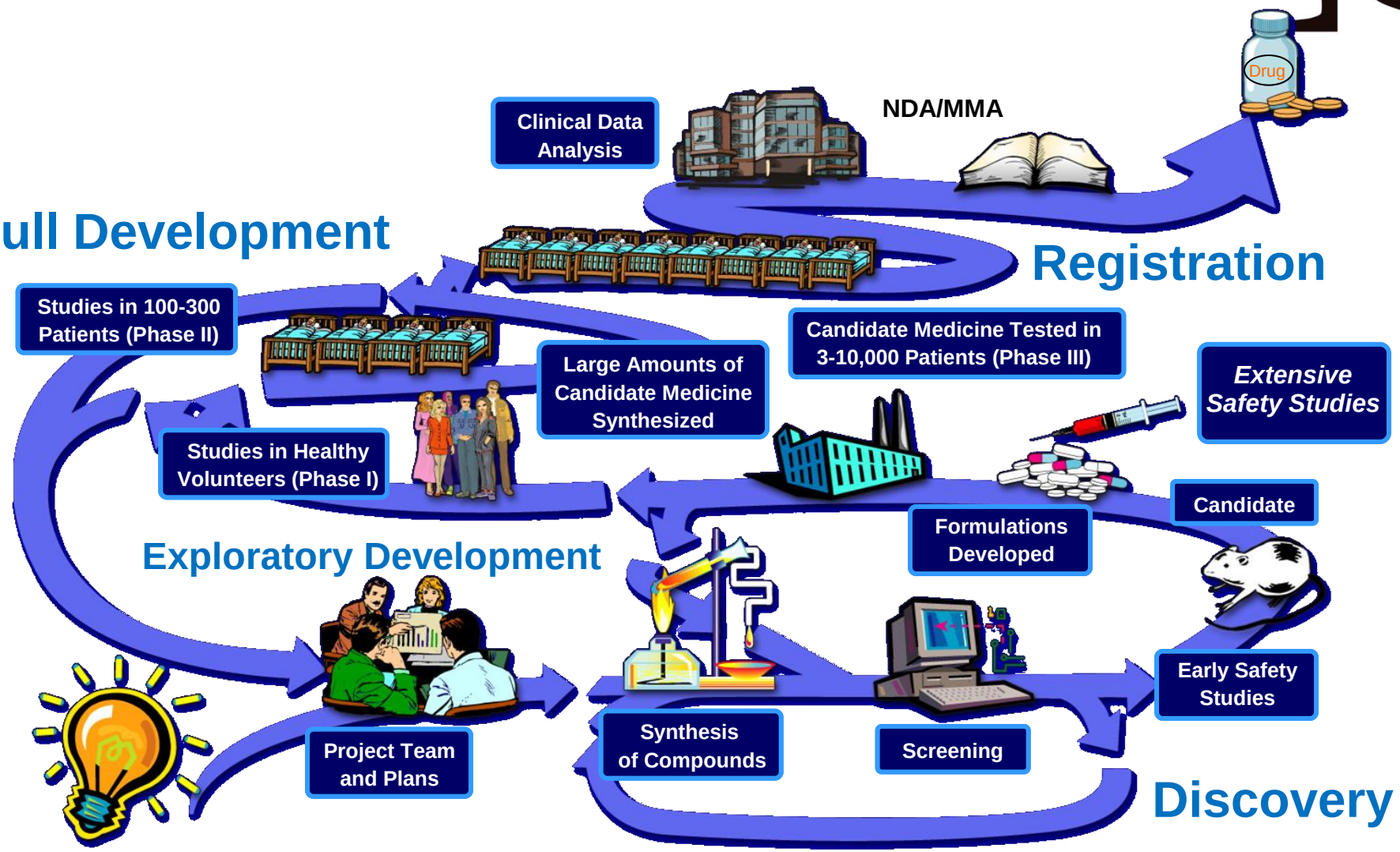
Drug Targets



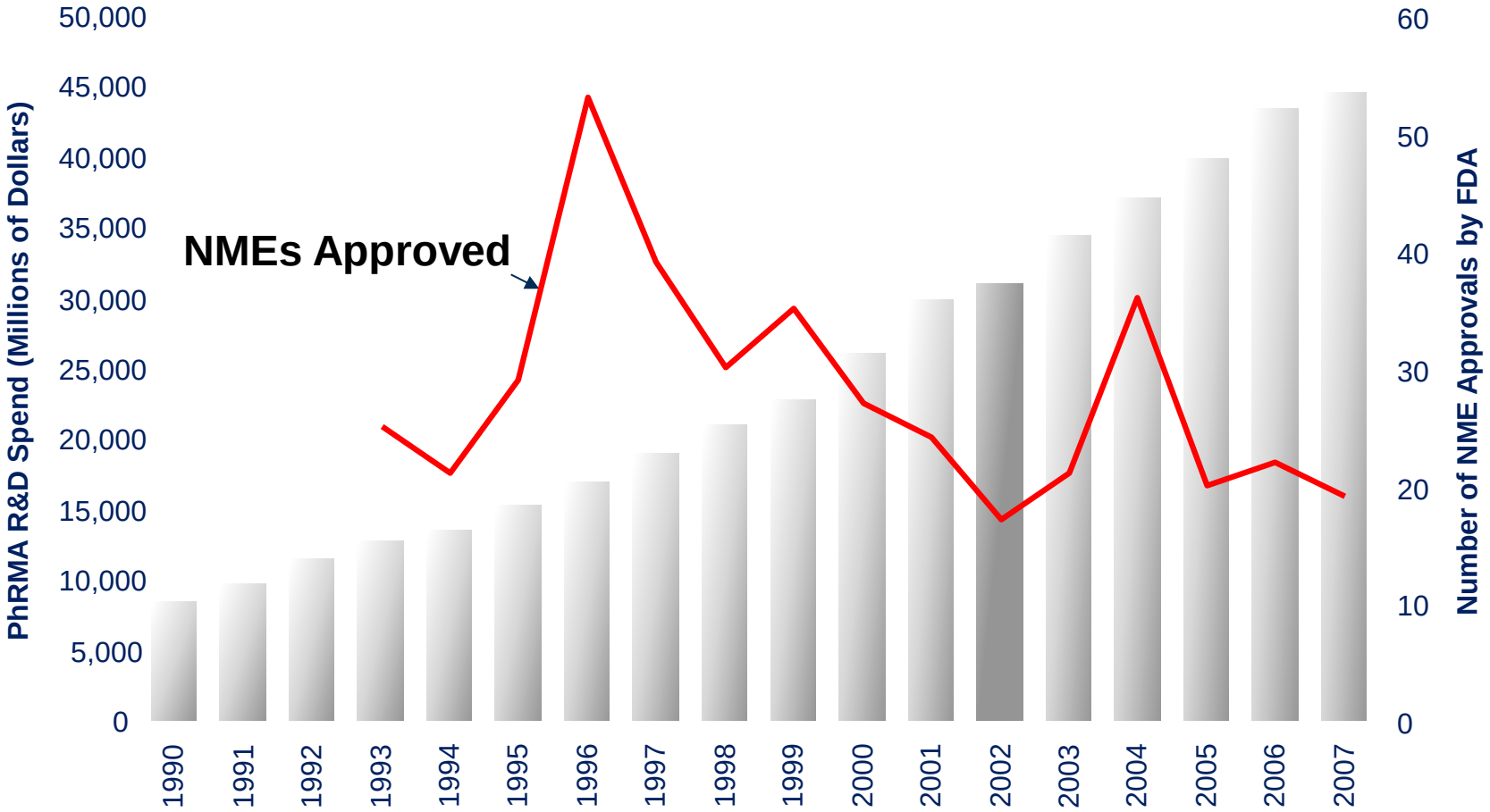
Developing a drug

You Decide

The Long Road to a New Medicine

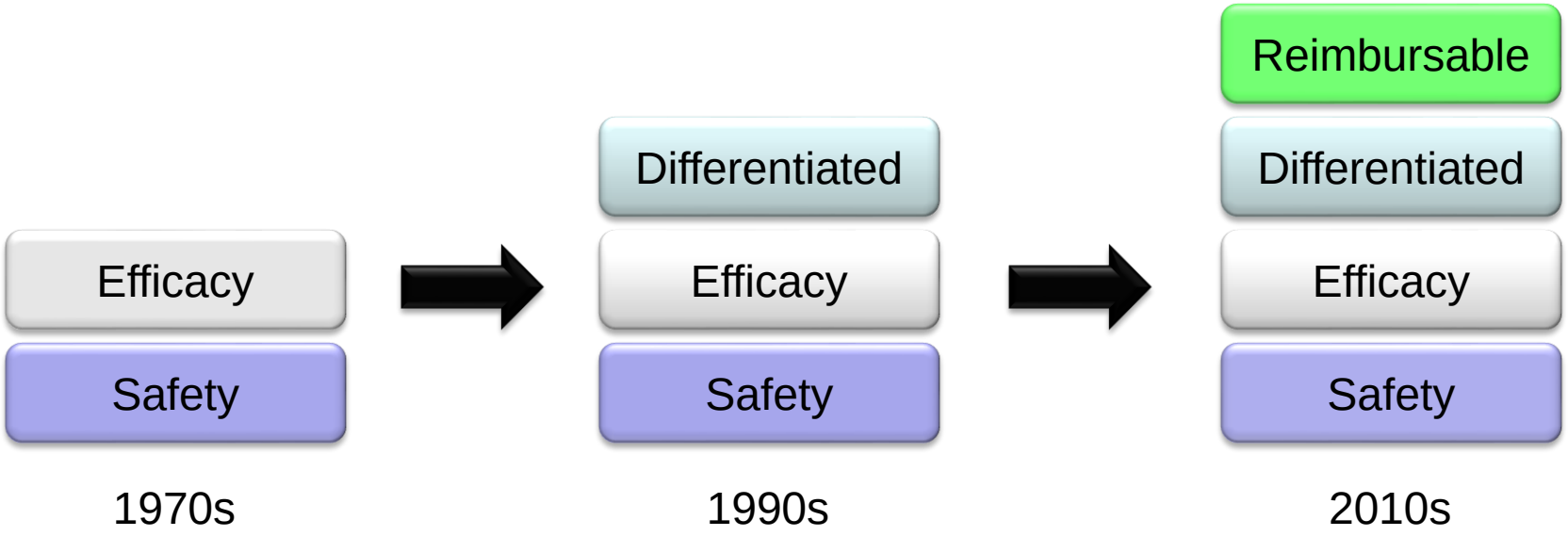


R&D Output Across The Industry is Flat…

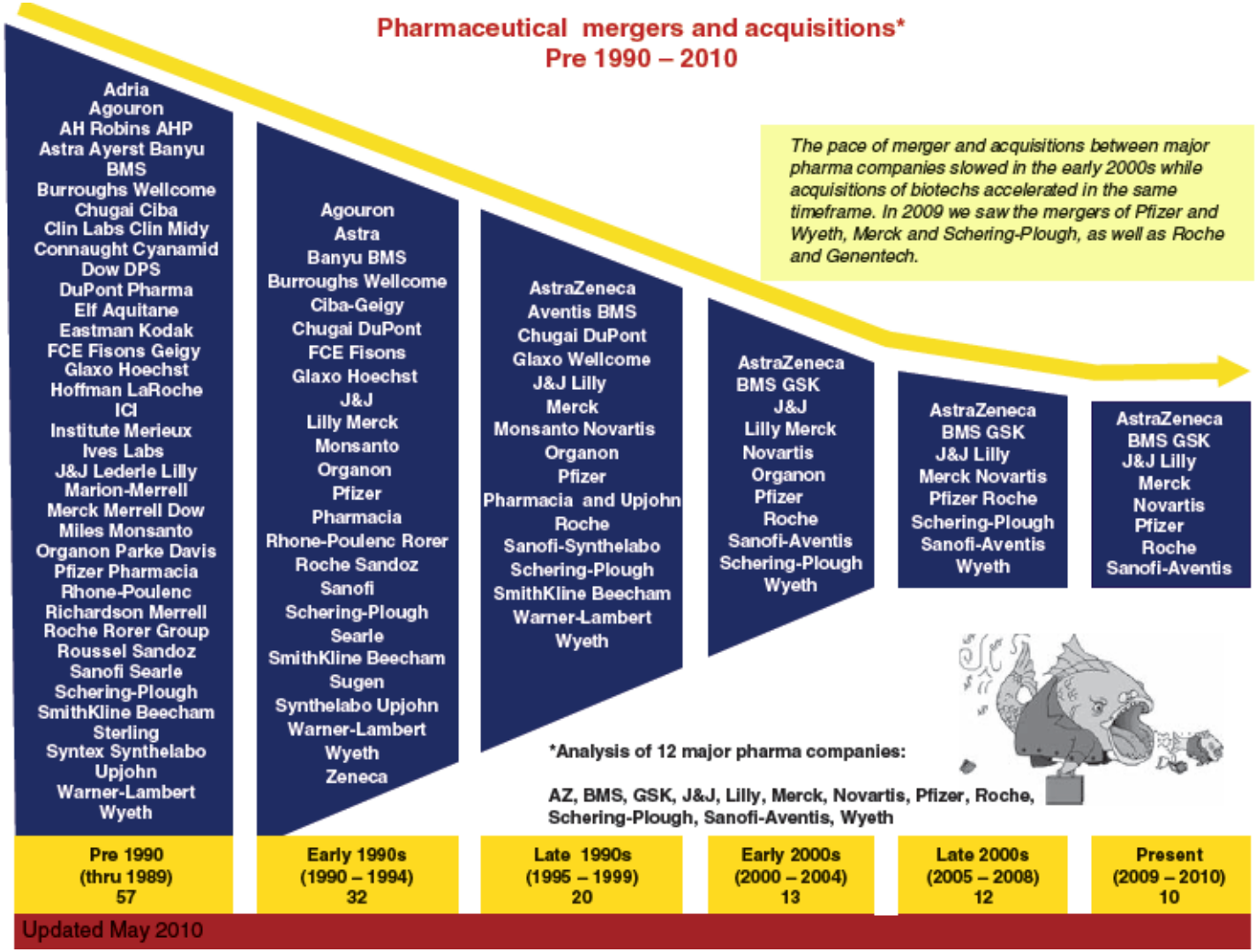


Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2008; CDER

Evolving nature of drug approvals



Consolidation Has Not Fixed The Problem



Source: Expert Opin Drug Discov 5:813-818 (2010)

Pharma R&D in Crisis?

SPECTRUM

A Service

Discovery and Innovation: Technologies, Strate

Barbara M. Bolten, M.S., M.B.A., Senior Program Manage

Rethinking Pharmaceutical R&D: Will New Strategies Yield a Pipeline

Barbara M. Bolten, M.S., M.B.A.

Decision Resources

"Pharmaceutical companies must rapidly reform R&D to n facing the industry. However, restructuring and shrinking R&D units is not enough to increase R&D productivity: companies must identify the right targets and efficiently implement new technology to discover novel, innovative drugs."

—Barbara M. Bolten, M.S., M.B.A., Senior Program Manager

Morgan Stanley

February 5, 2010

Industry View
Attractive

Pharmaceuticals

Research shrinkage. Even faster than we envisaged

Quick Comment – Impact on our views: Recent presentations at FY09 results by GSK and AZN support our recent industry thesis anticipating a much-accelerated shrinkage of significant parts of the small molecule research infrastructure, we believe. Given GSK and AZN comments, we expect Sanofi Aventis to outline a similar strategy at their results next week. We reiterate our thesis that small molecule

Morgan Stanley

January 20, 2010

Industry View
Attractive

Pharmaceuticals

Exit Research and Create Value

Still significant value in Pharma – we see material upside to ROIC, earnings and multiples as Pharma withdraws from most internal small molecule research and reallocates capital [illegible] sensing and

ANALYSIS

Nature Reviews Drug Discovery | AOP, published online 20 August 2010; doi:10.1038/nrd3230

Lessons from 60 years of pharmaceutical innovation

PERSPECTIVES

OUTLOOK

The case for entrepreneurship in R&D in the pharmaceutical industry

Nature Reviews Drug Discovery | AOP, published online 19 February 2010; doi:10.1038/nrd3078

ANALYSIS

How to improve R&D productivity: the pharmaceutical industry's grand challenge

Steven M. Paul, Daniel S. Mytelka, Christopher T. Dunwiddie, [illegible] C. Persinger, Bernard H. Munos, Stacy R. Lindborg and A[illegible] Schacht

Abstract | The pharmaceutical industry is under growing pressure from a range of environmental issues, including major losses of revenue owing to patent expirations,

REUTERS

Special Report: Big Pharma's stalled R&D machine

Wed, Jun 16 2010

By Ben Hirschler and Kate Kelland

LONDON (Reuters) - At just 28, Duncan Casey has already been from the university science bench to the world of Big Pharma research and back again. Now working in an Imperial College lab tucked behind London's famous Science Museum, he has no illusions about the prospects for researchers in the pharmaceutical industry.

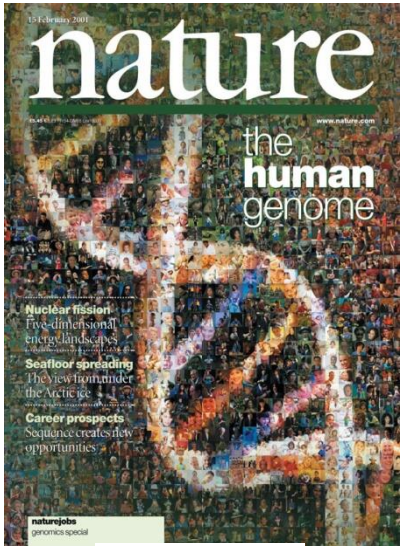
"The unit I used to work in -- GlaxoSmithKline's place in Harlow -- has been closed down now," says Casey, dressed in signature protective goggles and white coat as he works on synthetic chemistry. "It used to be a job for life. Now it's a job until the next restructuring."

Across the western world, Big Pharma is cutting back on the number of scientists it employs in its labs and the money it spends on research an[illegible]evelopment. Th drugs continues, but the men and women in white coats -- traditionally viewed as th[illegible]blood of the as untouchable as they once were.

How Does Pharma Emerge From The Crisis?

- New technology should provide the answers
  - Molecular biology
  - Genomics
  - Epigenetics

- Each advance produces more opportunities, and more challenges



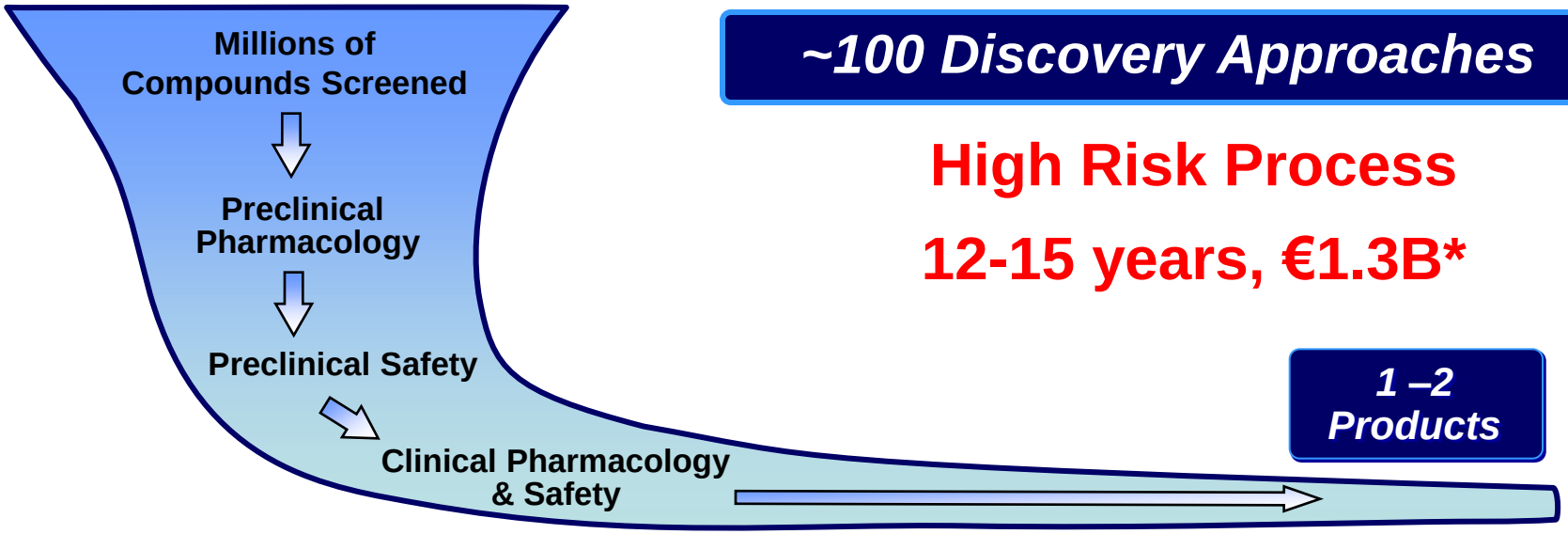
Feb, 2001

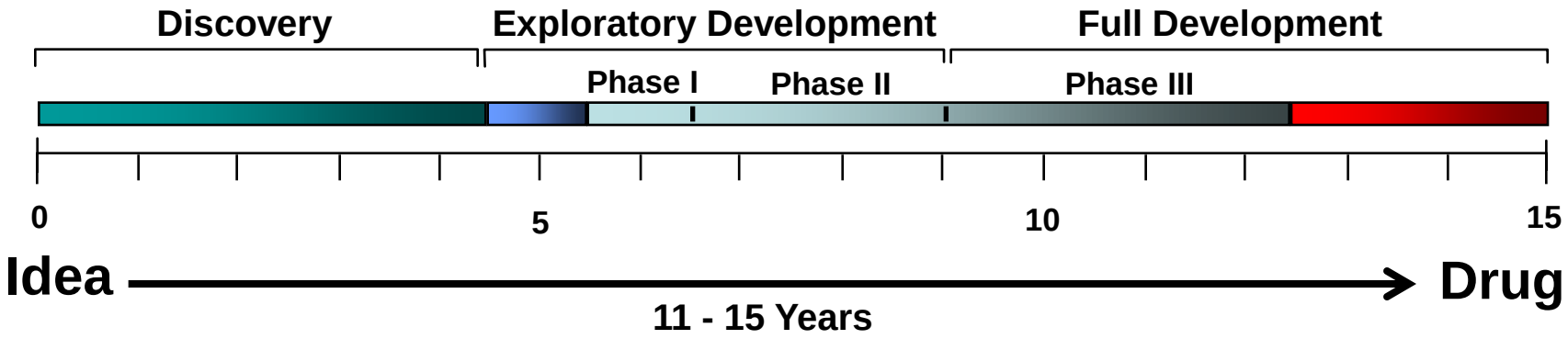
Feb, 2001

2011

"We should remember that genomics obeys the First Law of Technology: we invariably overestimate the short-term impacts of new technologies and underestimate their longer-term effects."
Francis Collins, NIH Director

Attrition is High in the R&D Process

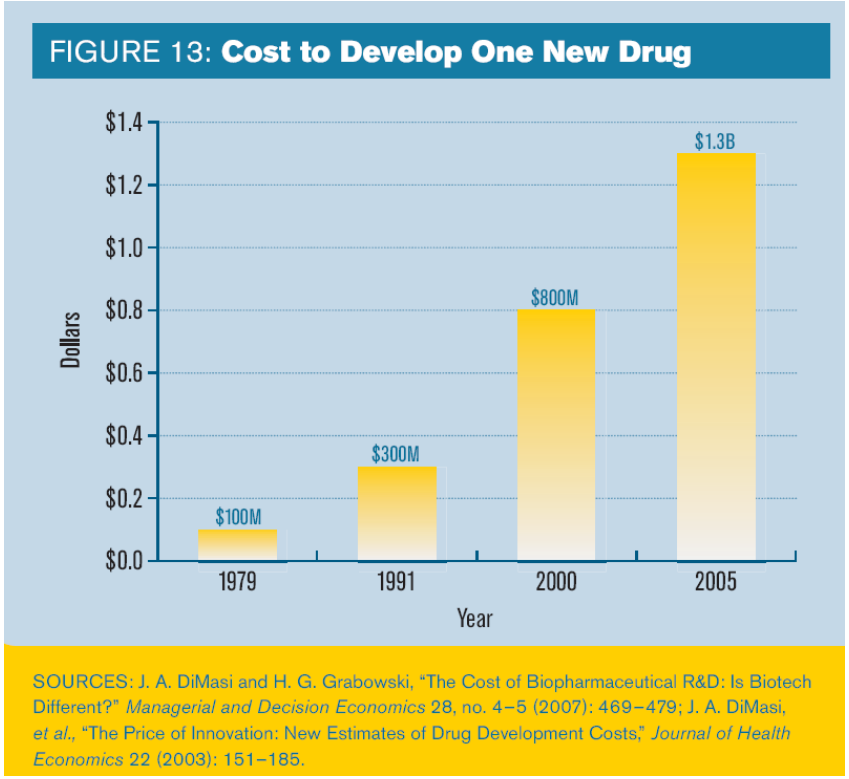




Source: DiMasi & Grabowski, Managerial Decision Econ, 2007;28:469-479

Costs of Drug Development

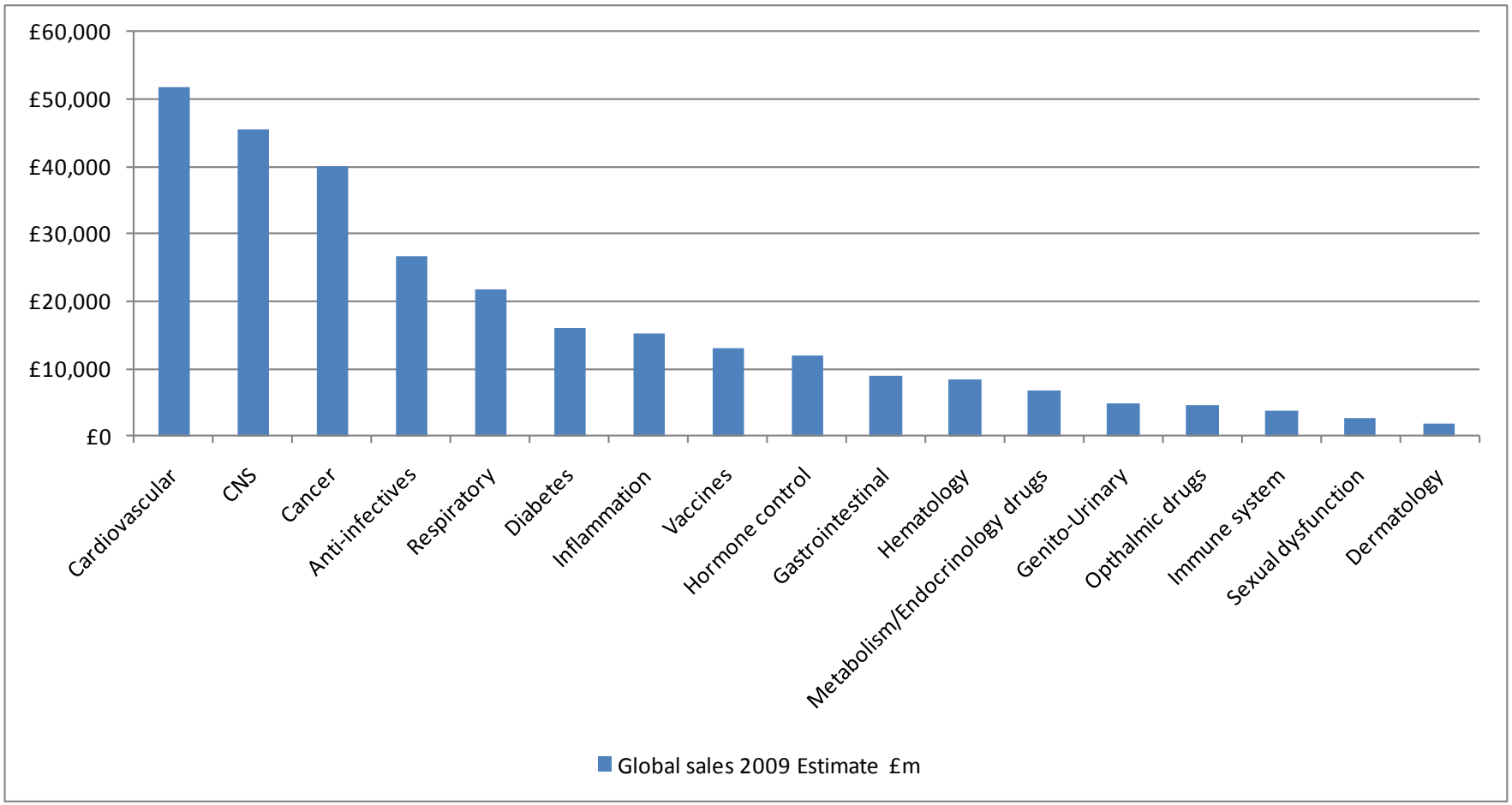
- Current cost of new drug
  - > £1billion
- Success rate
  - 1/10 per new compound
- Development Compounds
  - 1970 ~ 10
  - 1995 ~ 12
  - 2000 ~ 15
  - 2004 ~ 40
- Active Phase 1 R&D projects
  - 1998=521, 2008=1,265.
  - Technology driven productivity



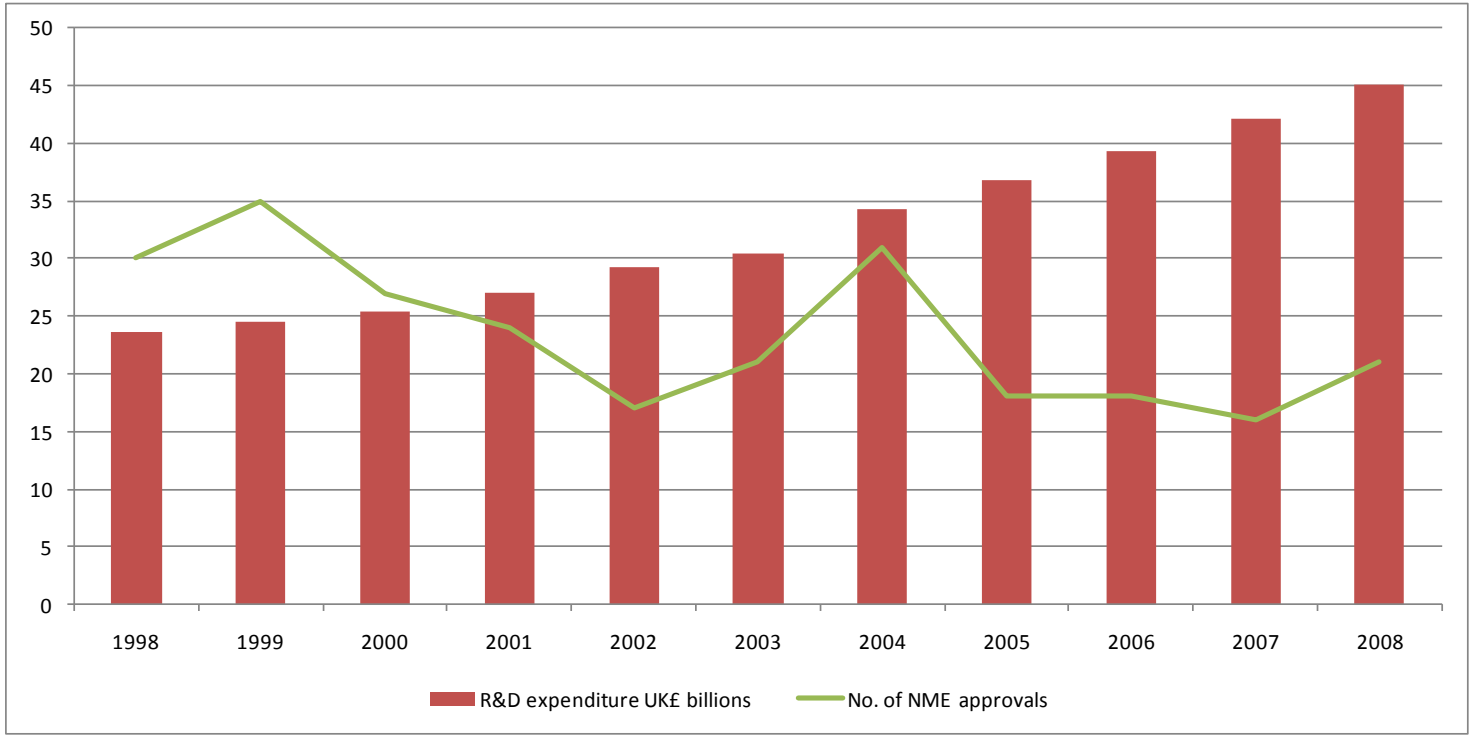
Bottlenecks

- Identifying new targets
- Preclinical safety
- Phase 1 clinical trials
  - Making Go No/Go decisions on adverse events and pharmacokinetics
- Phase 2 clinical trials
  - Making Go No/Go decisions based on efficacy

Sales in CNS estimated to exceed £45,000 million in 2009



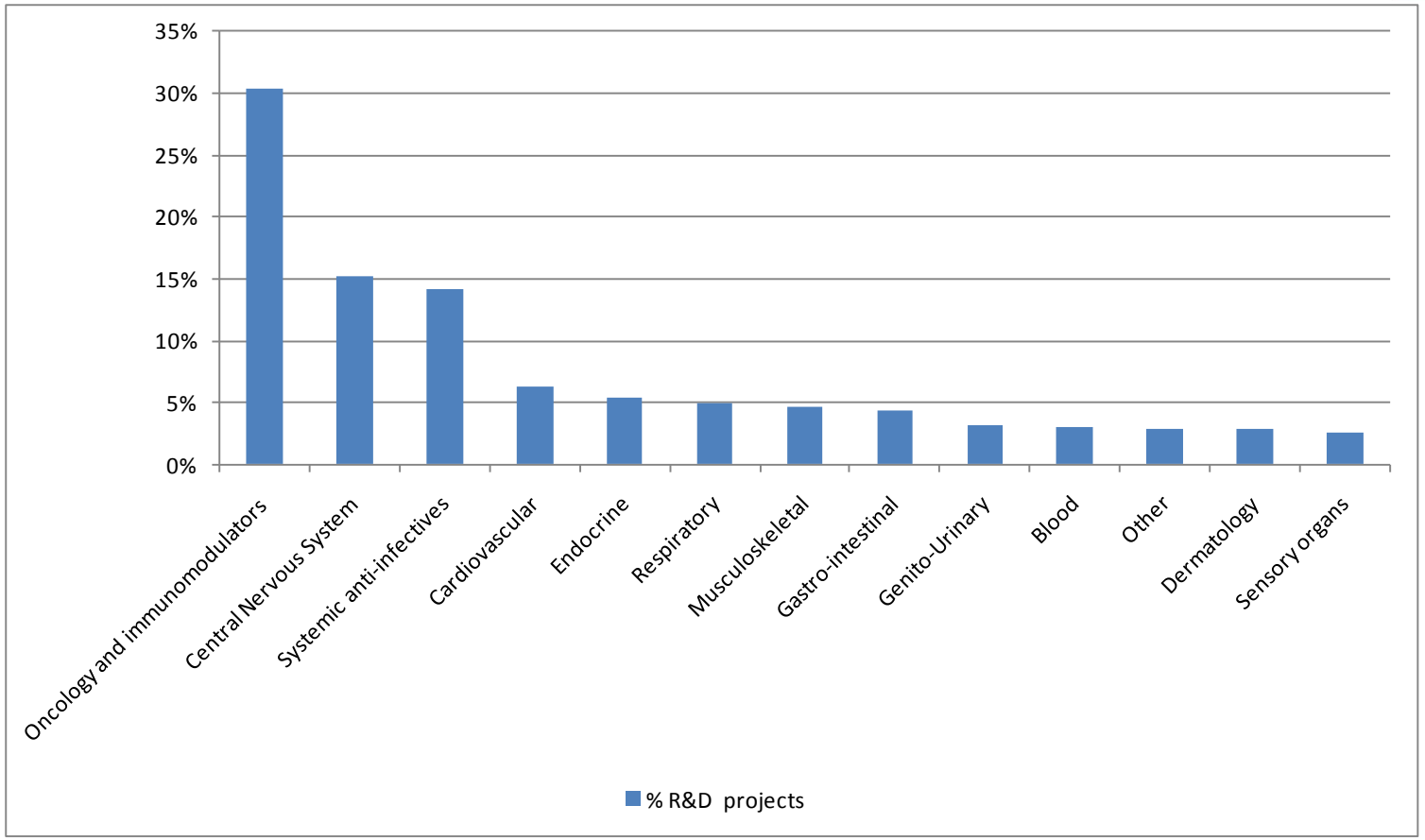
Source: (Lehmann Brothers Universe)



Source: CMR 2008 Factbook and CDER

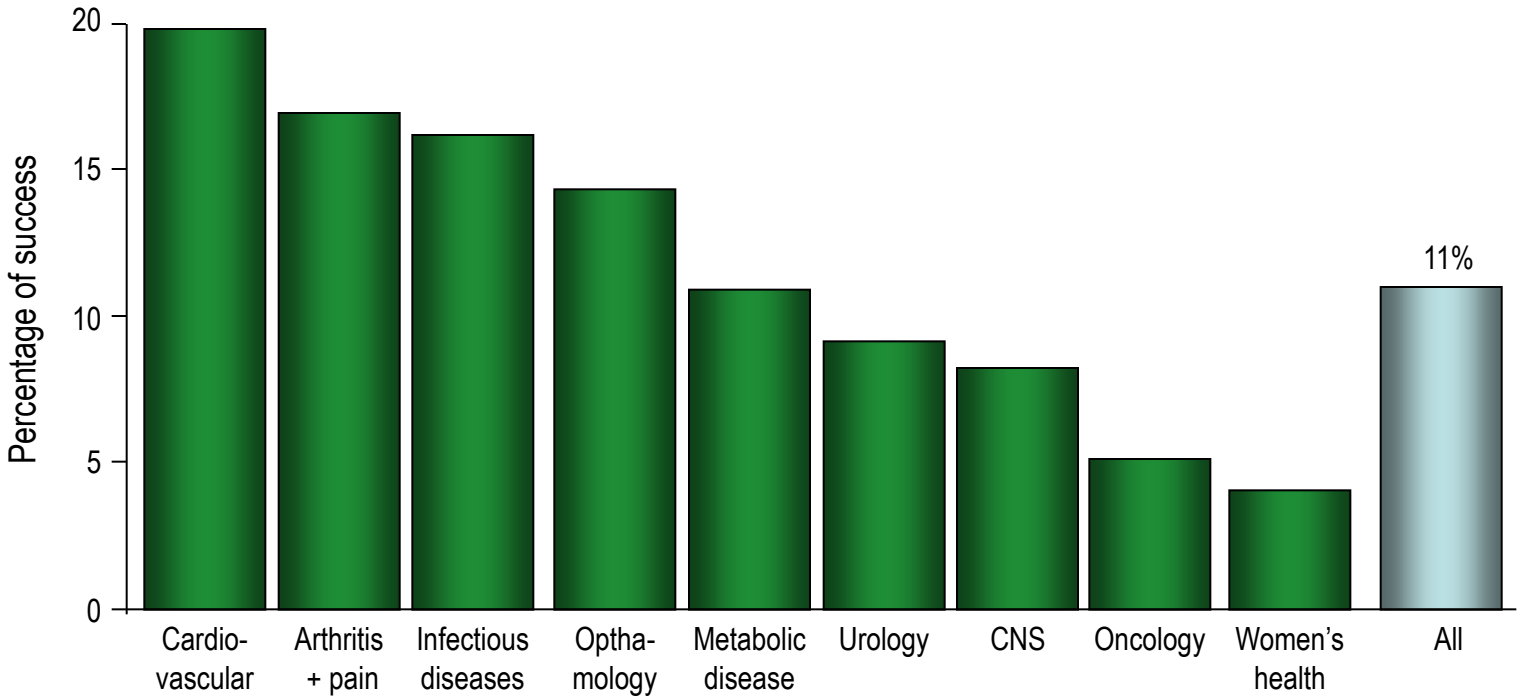
- The gap between R&D spend and NMEs is growing
- R&D spend was fuelled by sales of antidepressants and cardiovascular drugs
- Expectation was that neuroscience would deliver new NMEs

Oncology and CNS top therapeutic areas in R&D April 2009



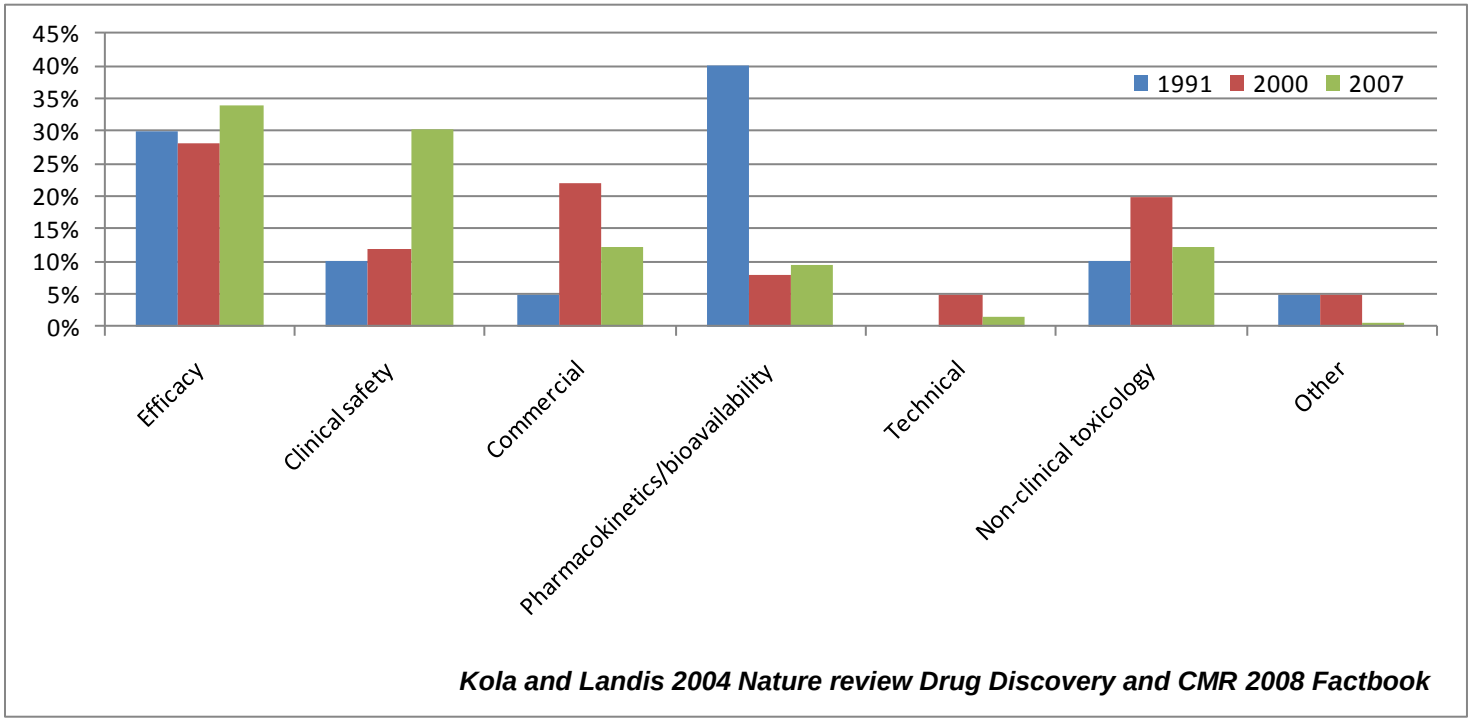
Source: EvaluatePharma April 2009

CNS has one of the lowest success rates



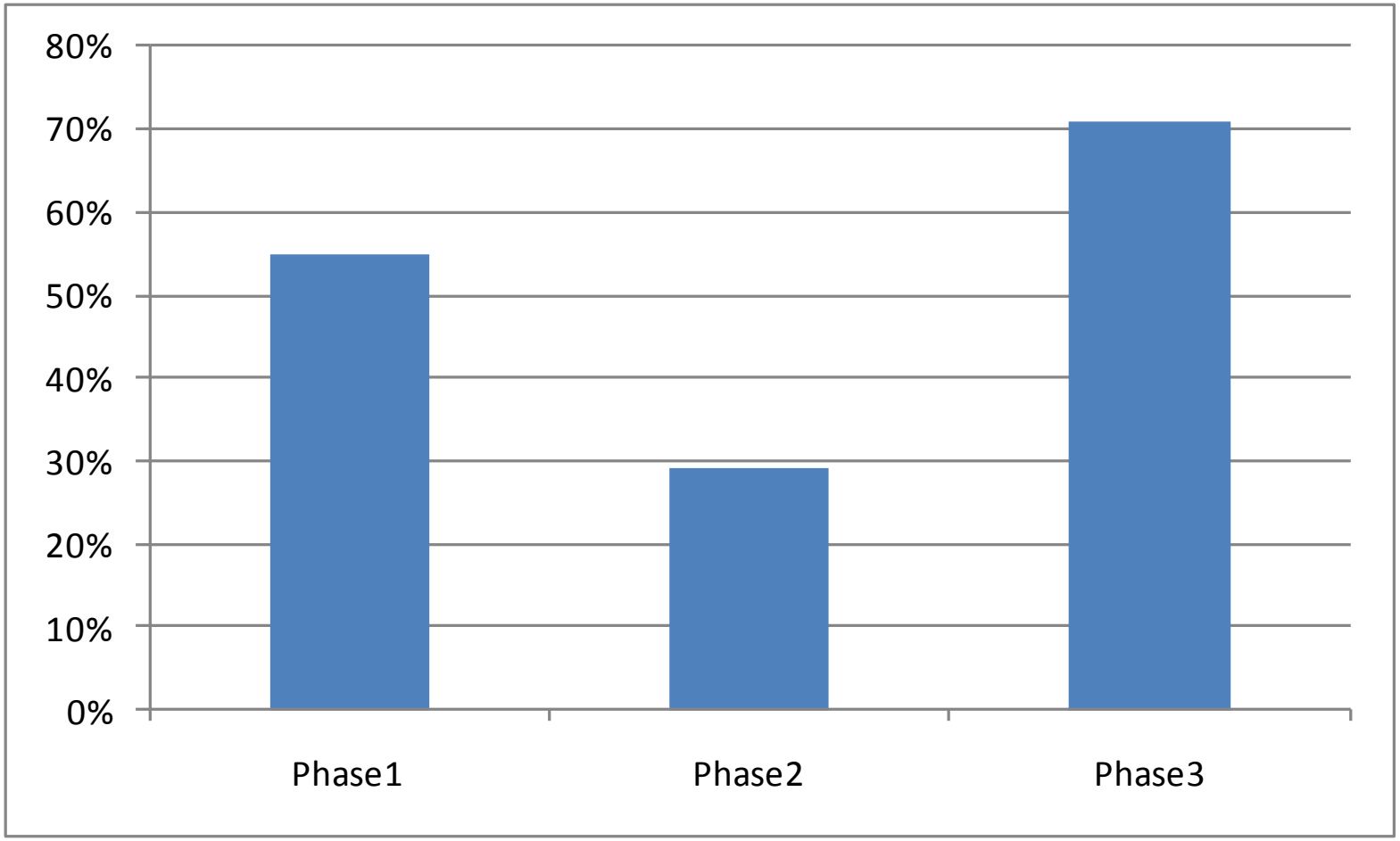
- Low percentage of success in CNS drug development second only to oncology and women's health

Lack of efficacy is the main reason for failure



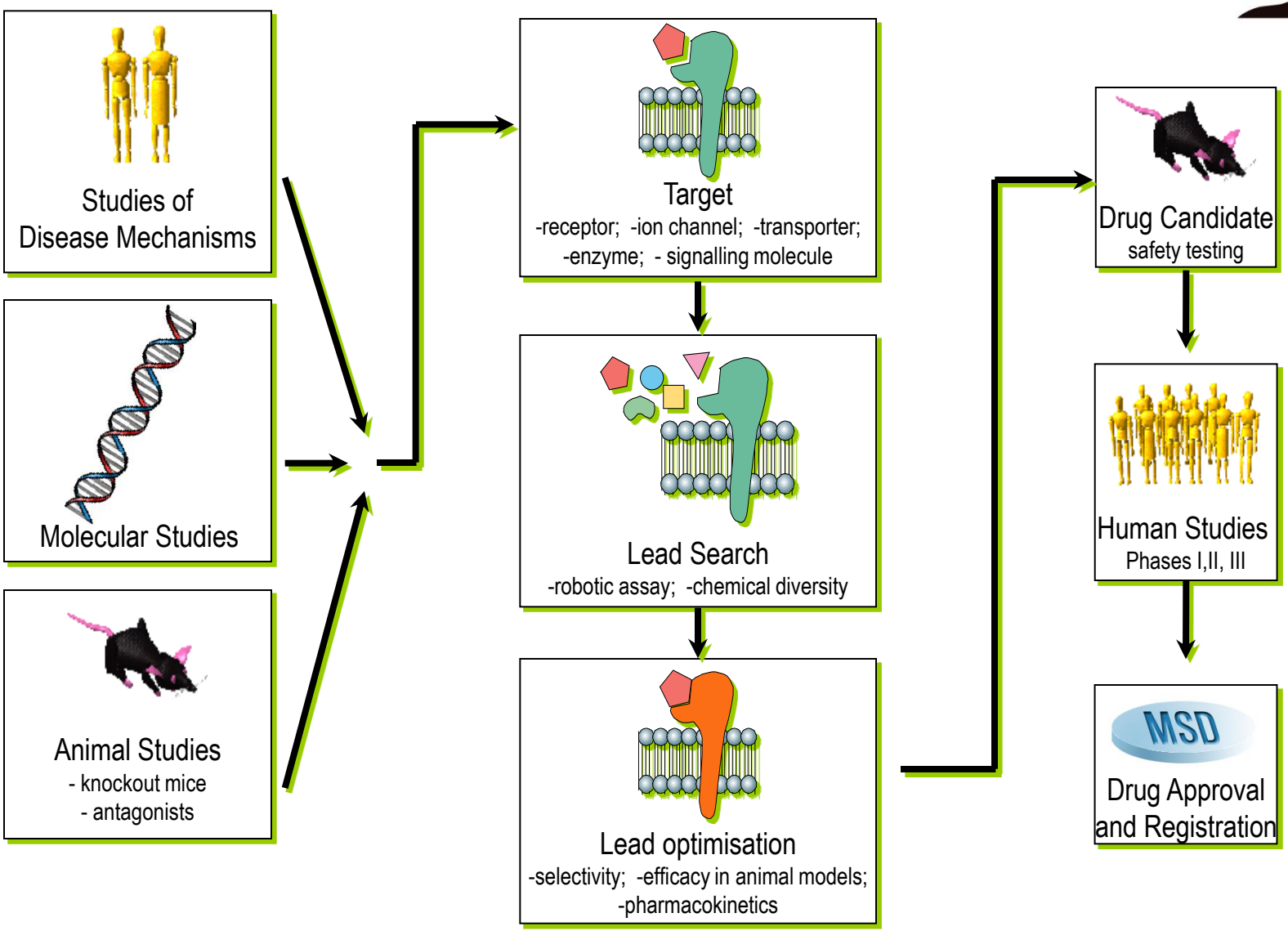
- In 1991 unpredictable PK was the main reason for failure
- In 2000 lack of efficacy was the main reason for failure
- In 2007 lack of efficacy remains the main reason for failure

Phase 2 has the lowest success rate



Source: CMR 2008 Factbook

The Drug Discovery Process



Research Project Selection

- Is there a medical need?
- Is there a rational scientific approach?
- What is the long-term perspective?
- What is the competitive environment?
- Do we have in-house expertise and resources?

Strategy for Drug Discovery

- Understand the molecular basis of a disease
- Select a therapeutic target (e.g. a ‘receptor’ in the brain)
- Link the therapeutic target to a defined mechanism of action
- Discover a compound that is safe, effective and novel

Drug Targets

- Current Targets of drugs in psychiatry/neurology
  - 15 Targets of currently used drugs
- Potential Targets
  - >80 Neurotransmitter/neuropeptide receptors
  - >30 Ion channels expressed by nerve cells
  - >160 Orphan GPCRs
  - >20 CNS specific transporters and enzymes

What are the *in vivo* properties of BZs?

BZs are:

Anxiolytic
Muscle Relaxant
Anticonvulsant
Hypnotic

BZs also:

Daytime somnolence
Interact adversely with ethanol
Impair memory
Induce dependence
Cause tolerance
Have abuse potential

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Do different GABA-A receptor subtypes mediate these various effects?

1. Using GABA-A subtype selective compounds

2. Generating transgenic mice insensitive to BZs at one or more subtype

Aims

Develop compounds that are:

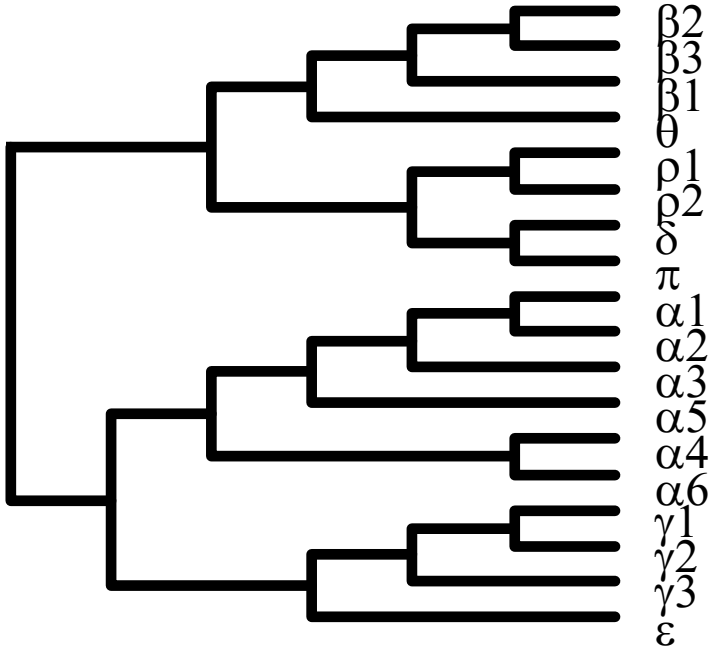
1. Agonists at α2/α3 subtypes
2. Have minimal effects at α1 or α5 subtypes

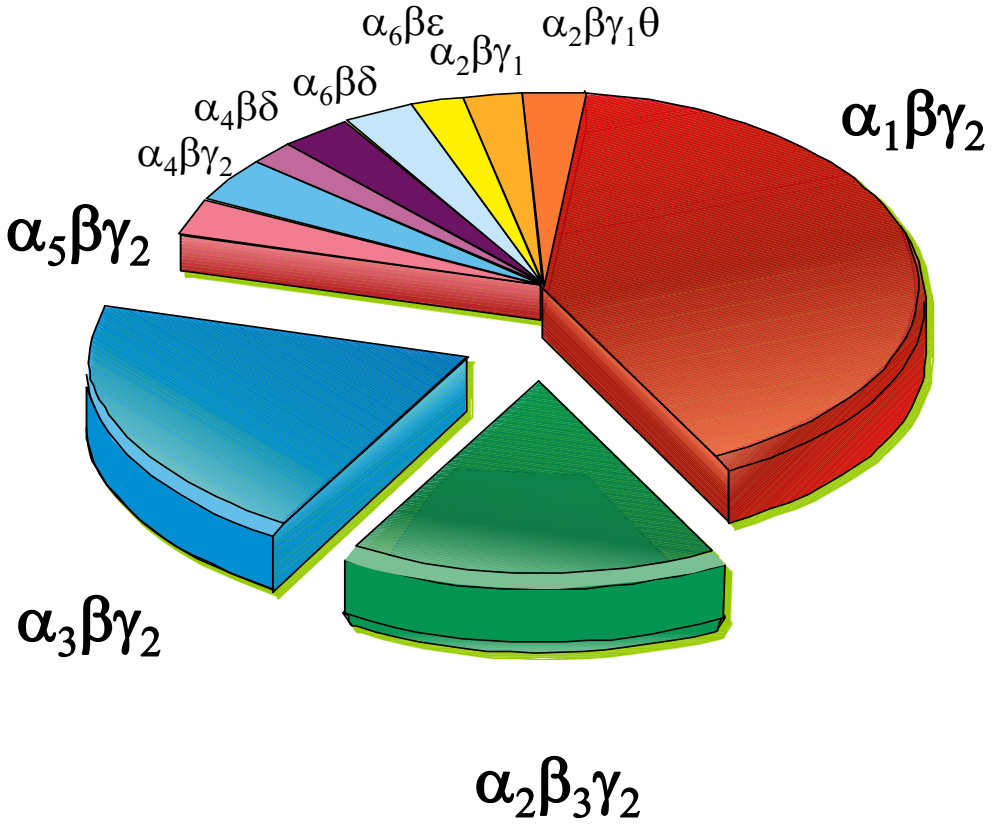
With the aim that:

1. Anxiolytic activity is retained, but
2. Daytime somnolence, amnesia, dependence and withdrawal are reduced

There are multiple GABA-A receptors subtypes in the brain

GABA$_A$ subunits

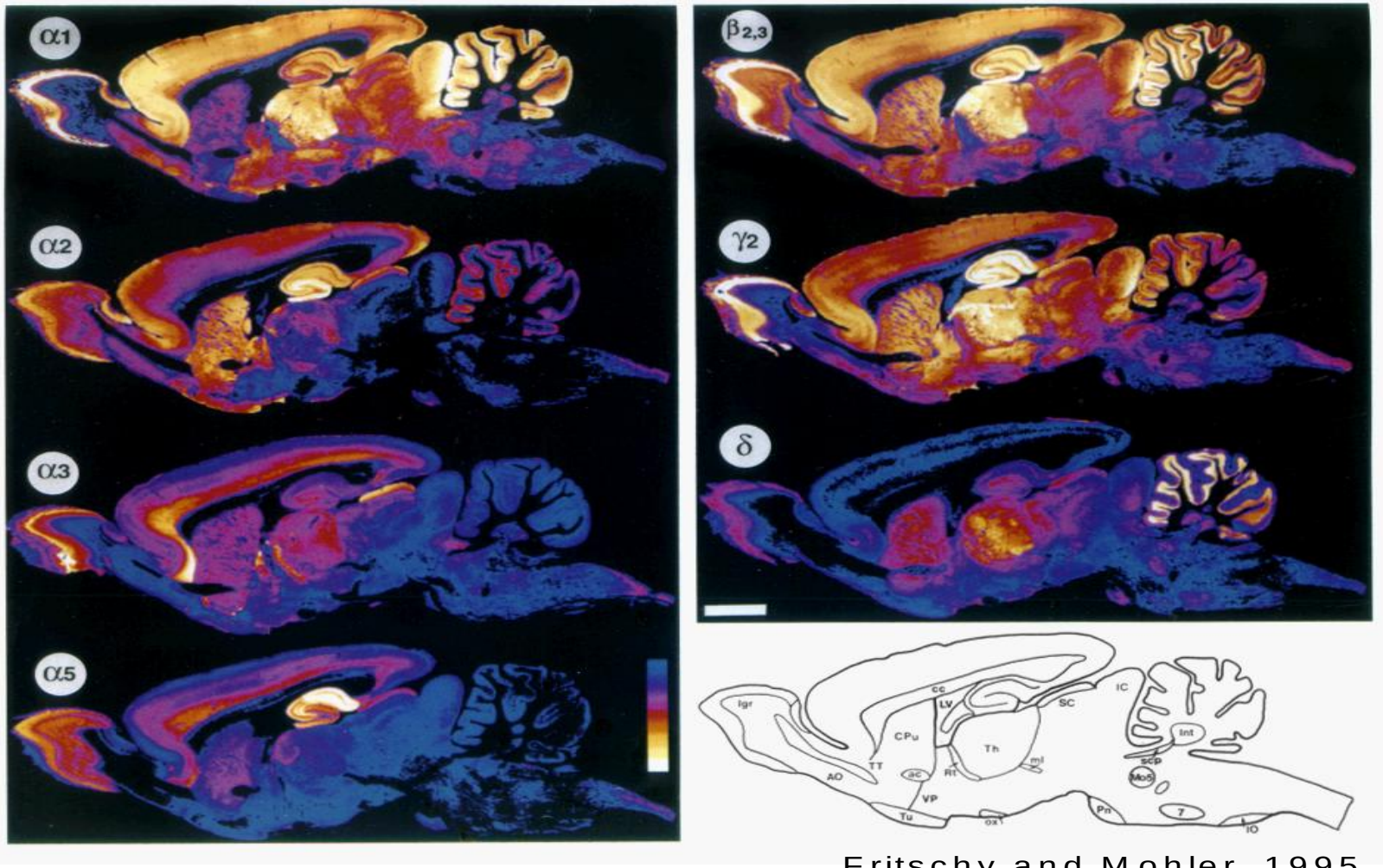




Some subtypes bind benzodiazepines

$\alpha_1\beta\gamma_2$ $\alpha_2\beta\gamma_2$ $\alpha_3\beta\gamma_2$ $\alpha_5\beta\gamma_2$

$GABA_A$ Receptors Containing α1, α2, α3 & α5 subunits have distinct distributions consistent with different functions



Fritschy and Mohler, 1995

α1 His101Arg Knock-in Mice

Subunit		Sequence		Diazepam binding
α1	86	NNLMASKIWTPDTFF**H**NGKKSVAHNMTMPNK	116	✓
α2	86	NNLMASKIWTPDTFF**H**NGKKSVAHNMTMPNK	116	✓
α3	111	NNLLASKIWTPDTFF**H**NGKKSMAHNMTTPNK	141	✓
α4	84	NNMMVTKVWTPDTFF**R**NGKKSVSHNMTAPNK	114	×
α5	90	NNLLASKIWTPDTFF**H**NGKKSIAHNMTTPNK	120	✓
α6	85	NLMNVSKIWTPDTFF**R**NGKKSIAHNMTTPNK	115	×
α1H101R	86	NNLMASKIWTPDTFF**R**NGKKSVAHNMTMPNK	116	×

Modified from Benson et al., (1998) FEBS Lett, 431:400-404

Rationale

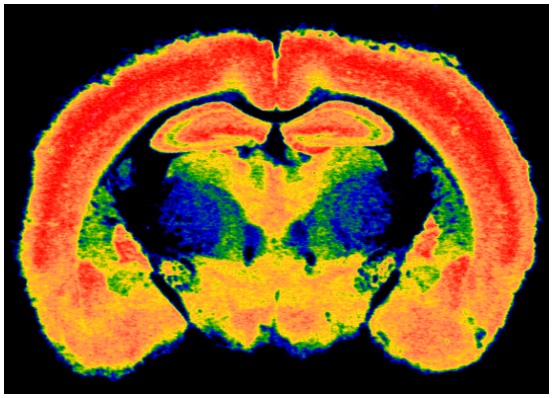
- Normal behaviour of knock-in mice should be the same as Wild Type mice
- When diazepam is administered, there is a loss of α1 subunit-mediated effects

Mouse	Diazepam-induced behaviours	Conclusion
WT	A + B + C + D	Normal behavioural profile
α1H101R	B + C + D	α1 containing $GABA_A$ receptors mediate behaviour A
α2H101R	A + C + D	α2 containing $GABA_A$ receptors mediate behaviour B
α3H126R	A + B + D	α3 containing $GABA_A$ receptors mediate behaviour C
α5H105R	A + B + C	α5 containing $GABA_A$ receptors mediate behaviour D

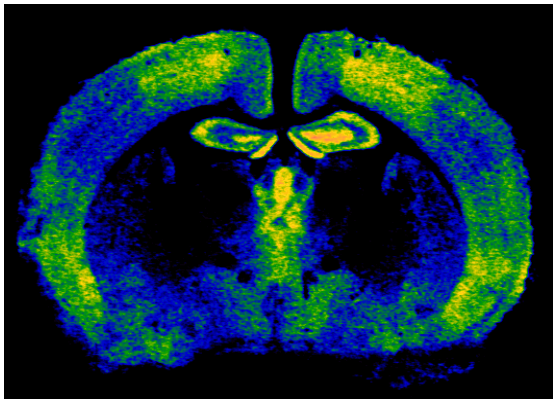
see also Rudolph et al., 1999, Nature, 401:796-800

BZ Binding Sites Decrease in α1H101R Knock-in Mice

	Wild Type mice					
Compound	α1	α2	α3	α4	α5	α6
Diazepam (Valium®)	✓	✓	✓	×	✓	×
[3H]Ro 15-1788 (flumazenil)	✓	✓	✓	×	✓	×
[3H]Ro 15-4513	✓	✓	✓	✓	✓	✓
[3H]Ro 15-4513 + diazepam	×	×	×	✓	×	✓



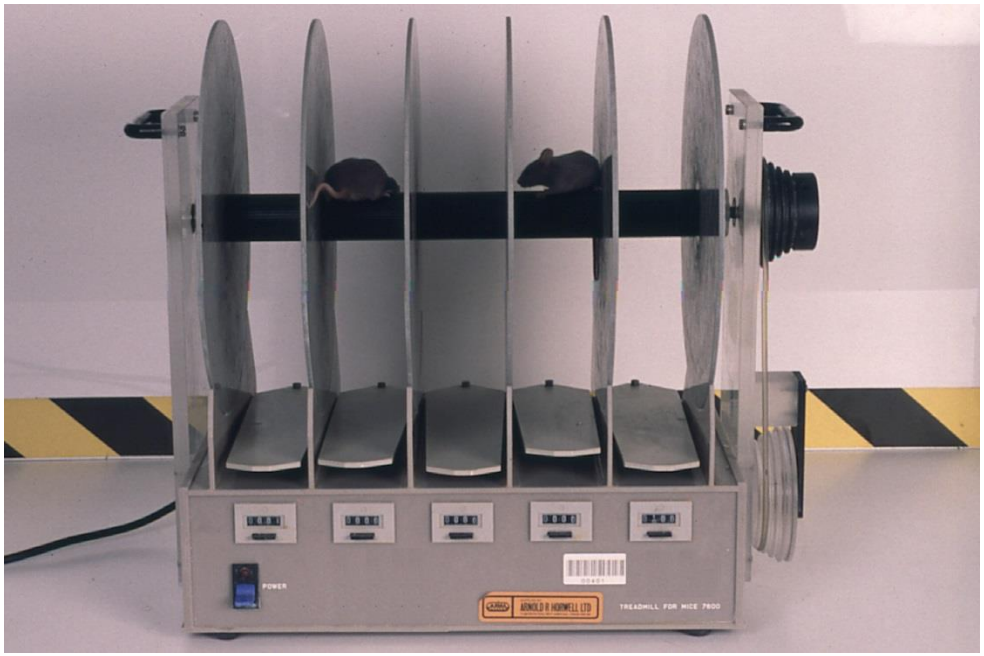
	α1 His101Arg mice					
Compound	Hα1R	α2	α3	α4	α5	α6
Diazepam (Valium®)	×	✓	✓	×	✓	×
[3H]Ro 15-1788 (flumazenil)	×	✓	✓	×	✓	×
[3H]Ro 15-4513	✓	✓	✓	✓	✓	✓
[3H]Ro 15-4513 + diazepam	✓	×	×	✓	×	✓

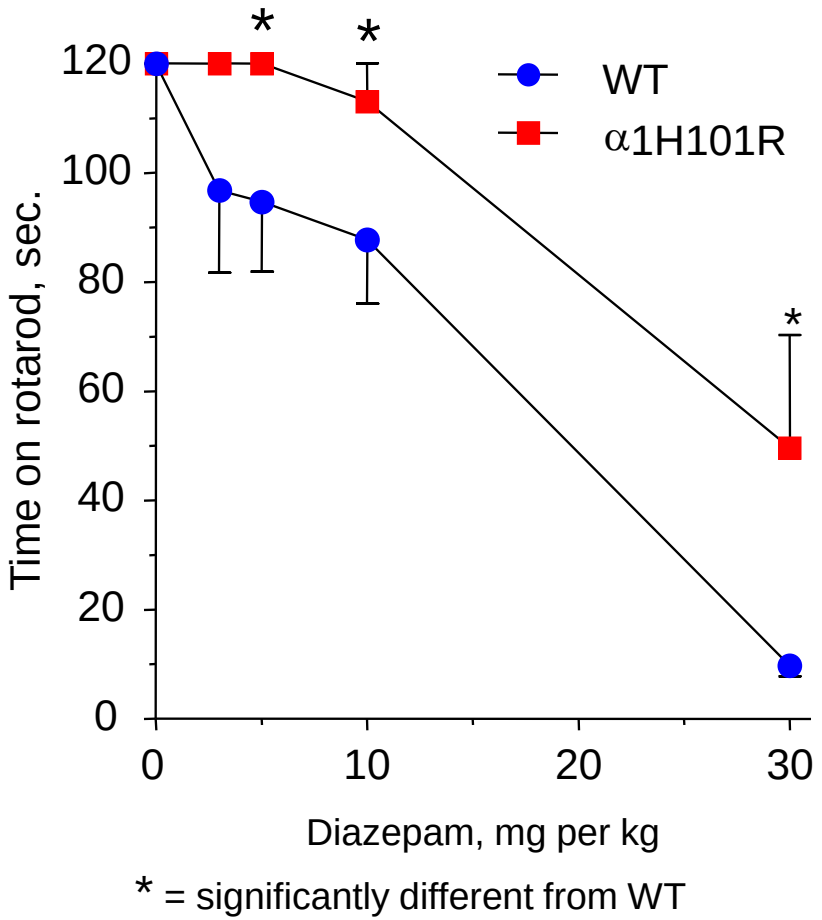


- Total number of $GABA_A$ receptors unaltered
- α1H101R receptors have normal GABA response

Diazepam is Less Sedating in α1H101R Mice

- Mice trained to walk on rotarod for 2 min
- Latency to fall off or complete trial (120 sec.) is recorded after dosing

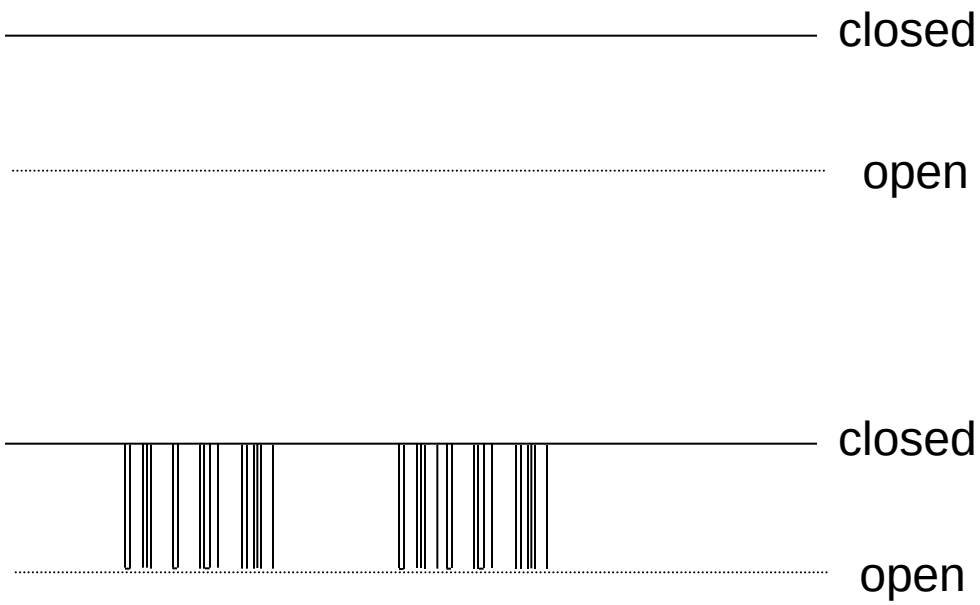




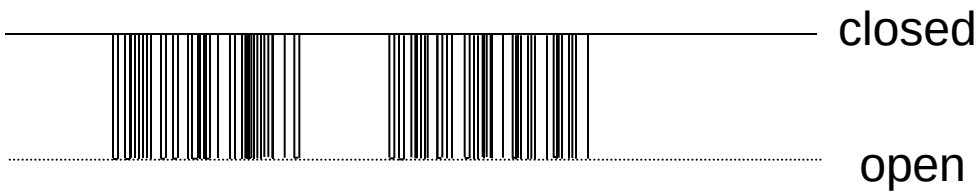
- α1-containing $GABA_A$ receptors play a role in sedation

What happens when a GABA molecule binds?

Cl^-



What happens when a BZ molecule binds?



- BZ agonist increases GABA binding site affinity
- BZ agonist increases probability of channel opening while agonist is bound

Make a compound that does not ***bind*** to α1

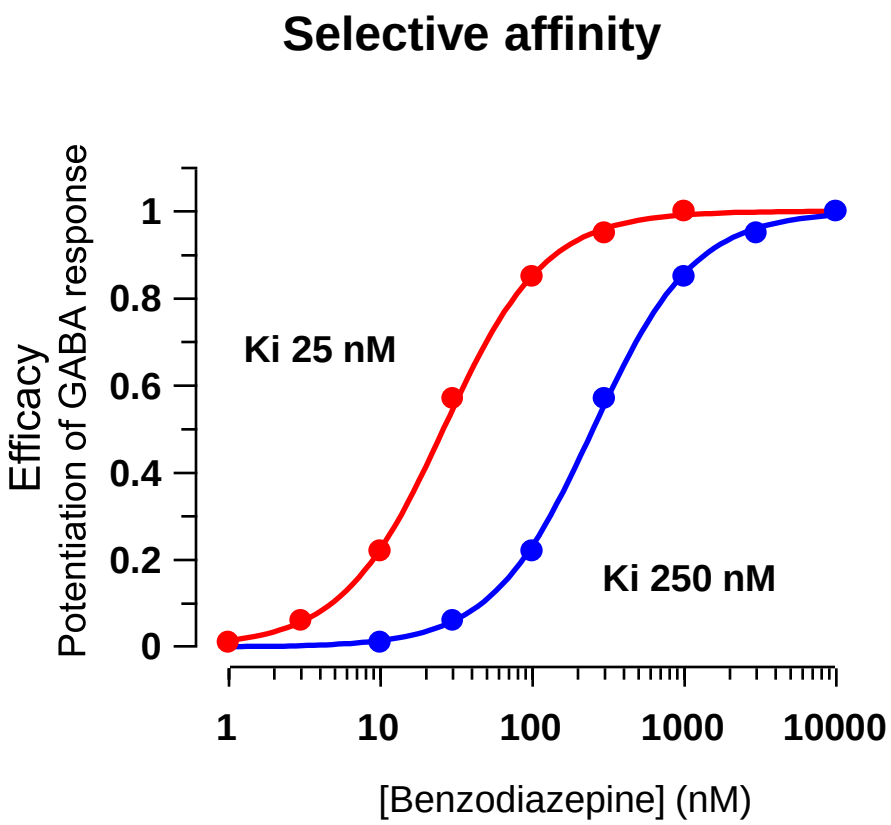
- Place your bets – stake €10M

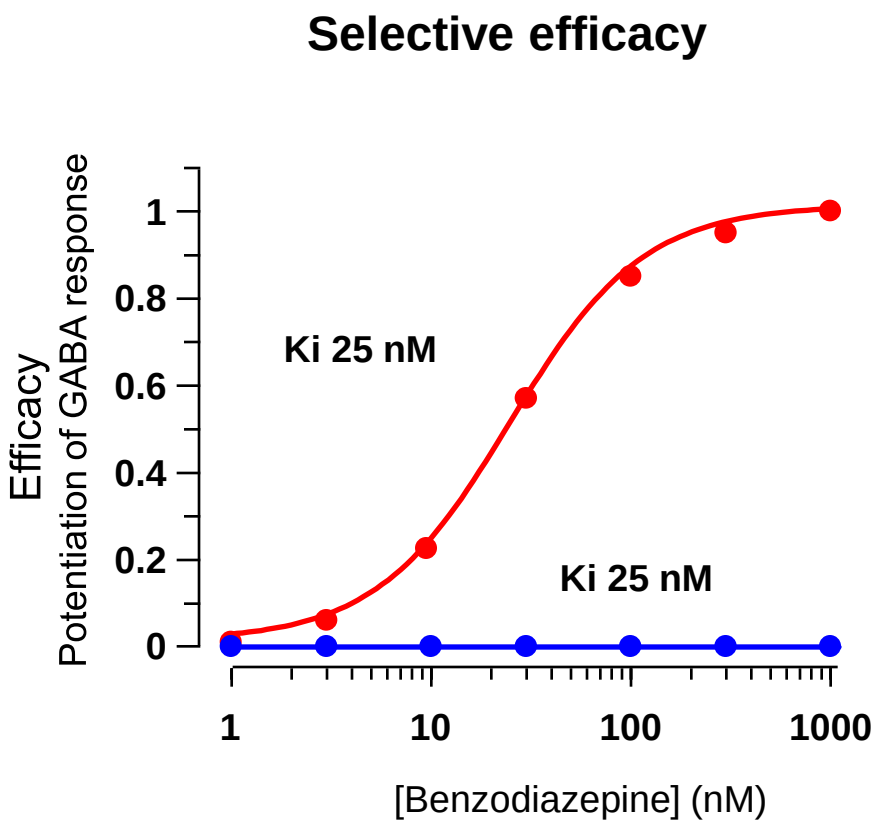
Make a compound that does not ***bind*** to α1

- Place your bets – stake €10M

You lose! – not possible to make an α1 selective compound

A compound can have selective affinity or efficacy





Make a compound that has selective efficacy

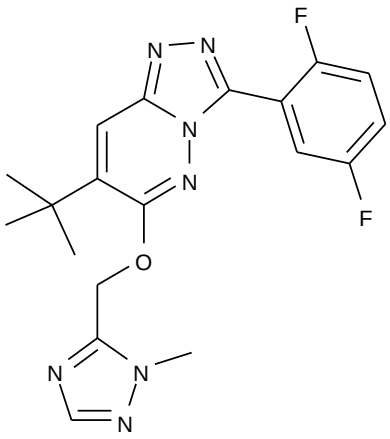
- Place your bets – stake €30M

Make a compound that has selective efficacy

- Place your bets – stake €30M

You win! – It is technically possible but takes 3 years

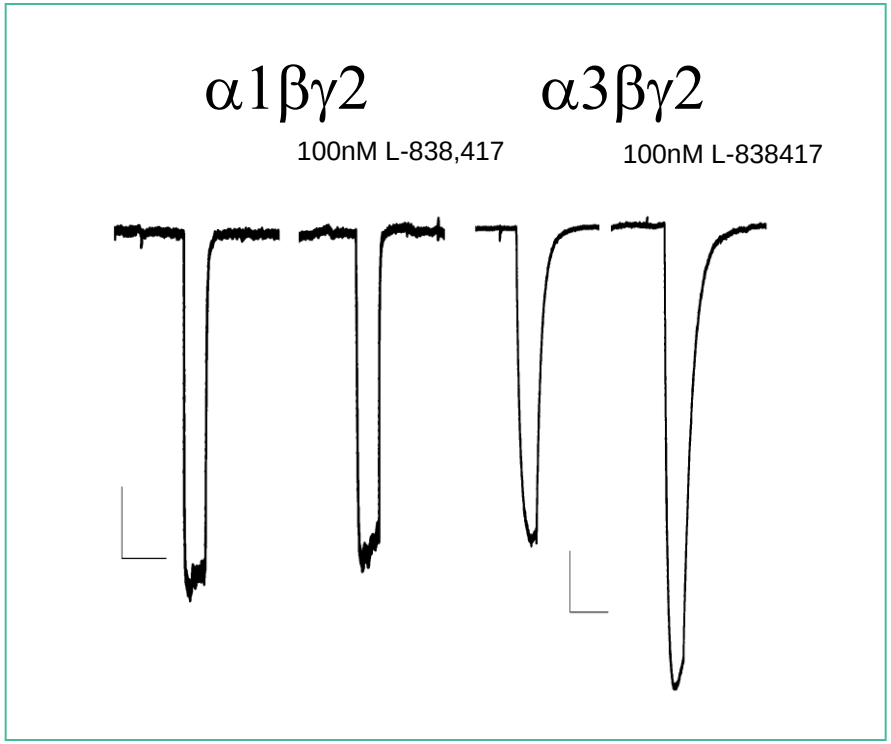
L-838,417 has high affinity for BZ-sensitive $GABA_A$ receptors

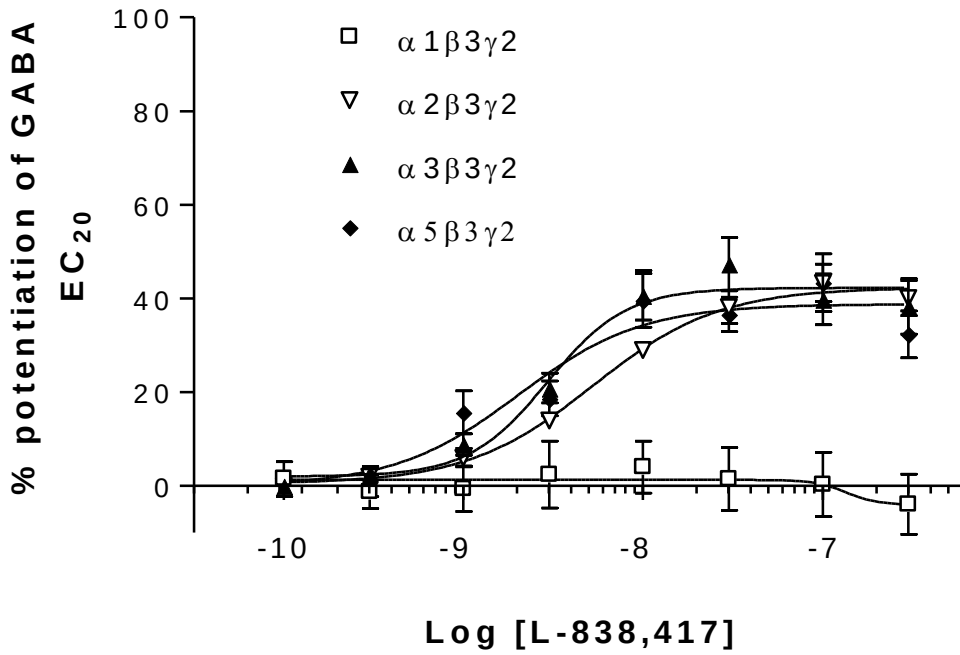


L-838,417

Receptor combination	Binding Ki (nM)
$\alpha1\beta3\gamma2$	0.8
$\alpha2\beta3\gamma2$	0.7
$\alpha3\beta3\gamma2$	0.7
$\alpha4\beta3\gamma2$	267
$\alpha5\beta3\gamma2$	2.2
$\alpha6\beta3\gamma2$	2183
Mouse brain	1.2

….but is an antagonist at the α1-subtype

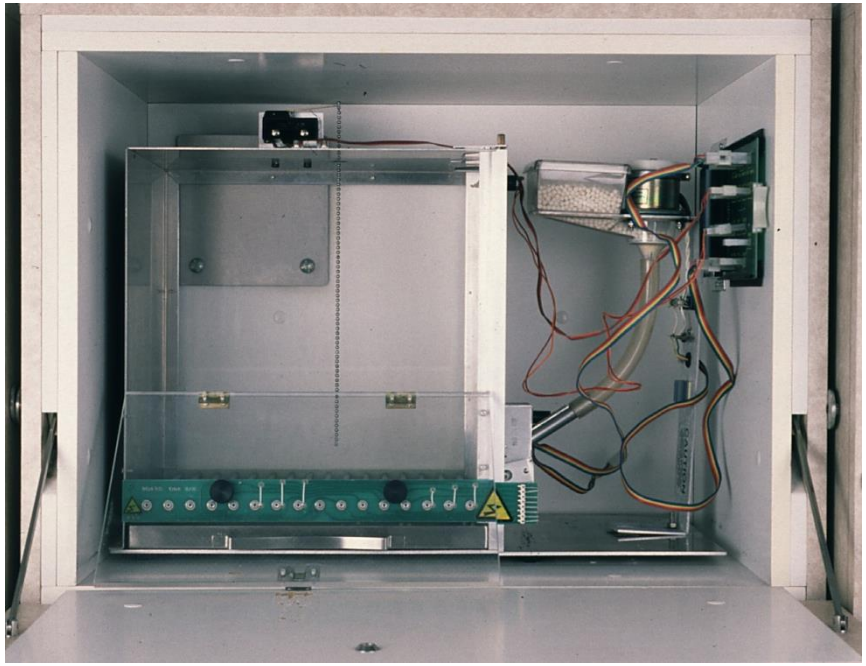


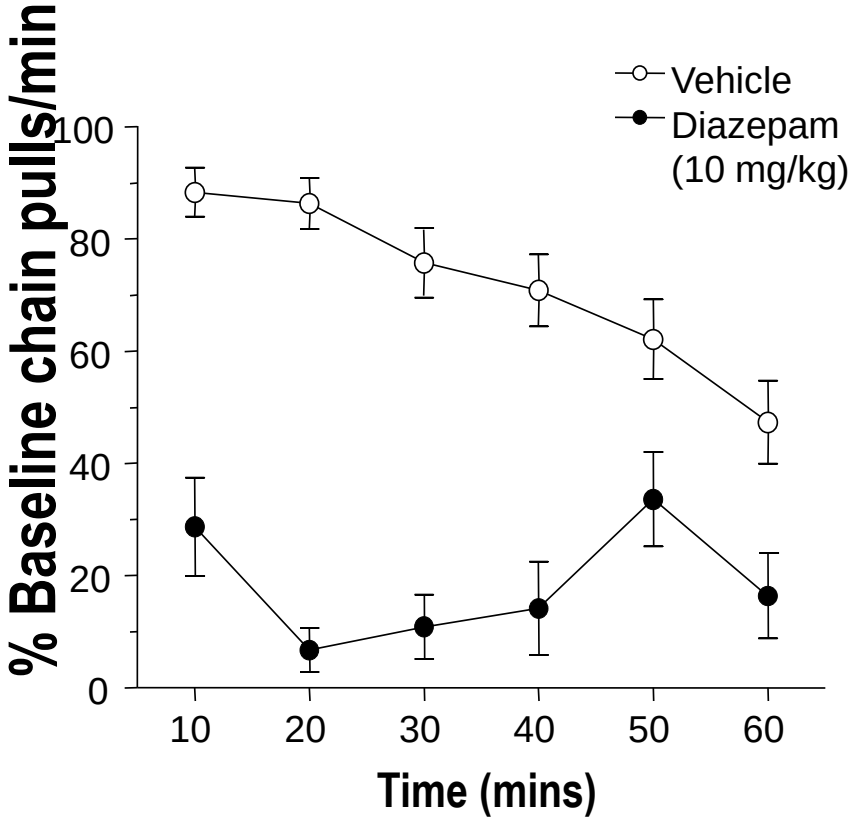


Sub nM affinity for BZ-sensitive $GABA_A$ receptors

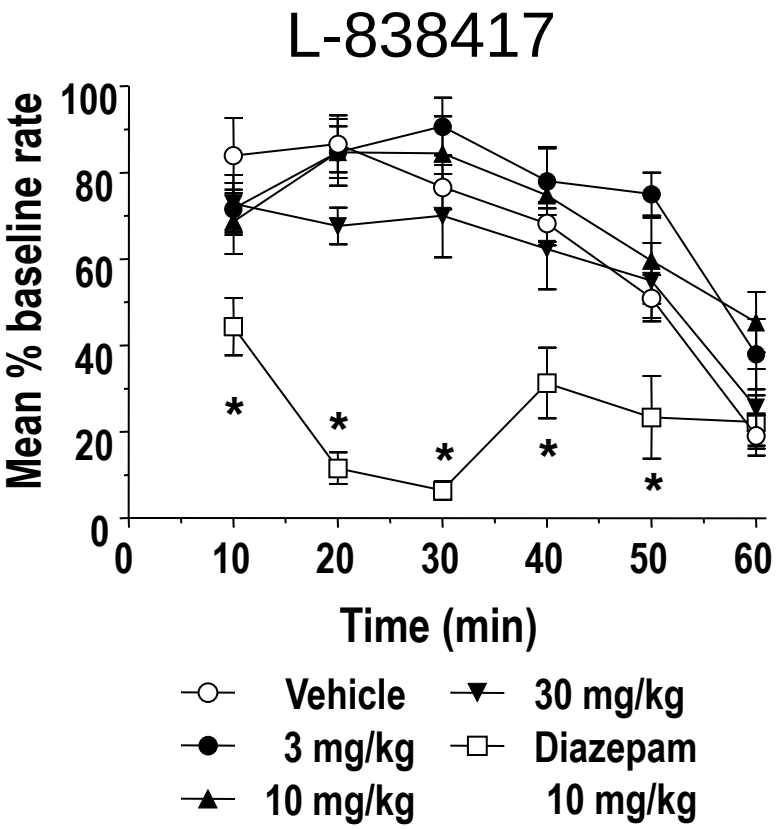
	Efficacy % relative to diazepam		
Receptor combination	L-838417	TPA123	TPA023
$\alpha 1\beta 3\gamma 2$	0	20	0
$\alpha 2\beta 3\gamma 2$	40	40	15
$\alpha 3\beta 3\gamma 2$	40	40	30
$\alpha 5\beta 3\gamma 2$	40	40	<5

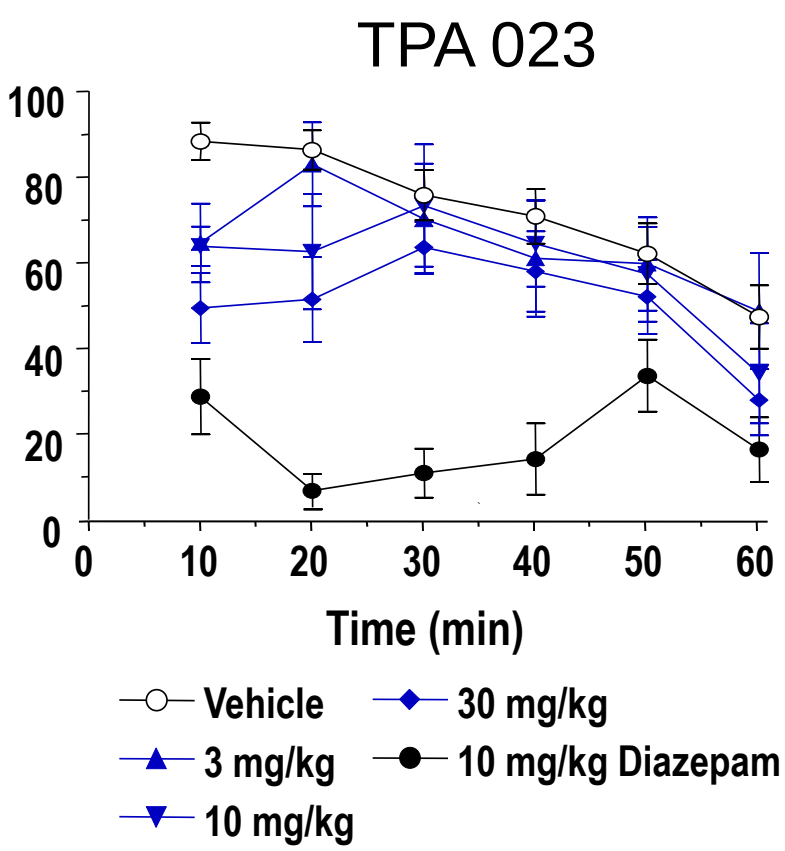
Diazepam rate decreasing effects in the rat chain-pulling test





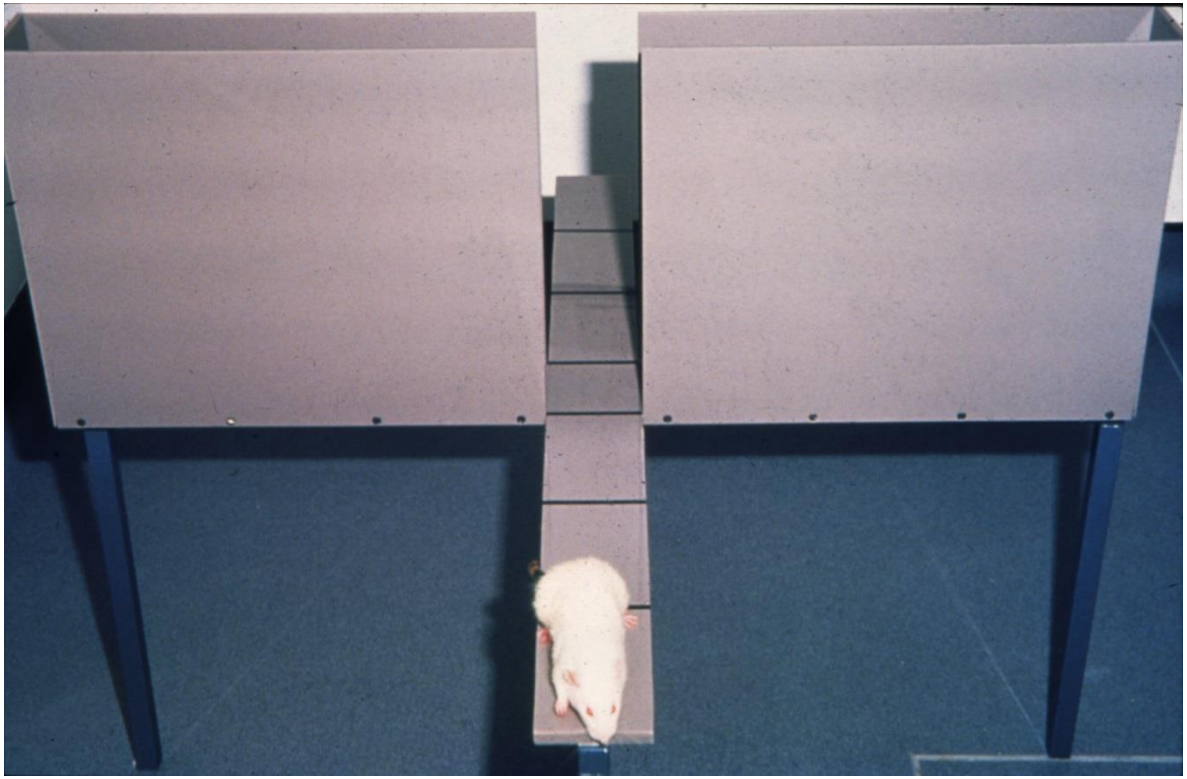
Subtype selective compounds do not reduce response rates in the rat chain-pulling test





α1 **is** responsible for rate reducing effects but are anxiolytic effects retained?

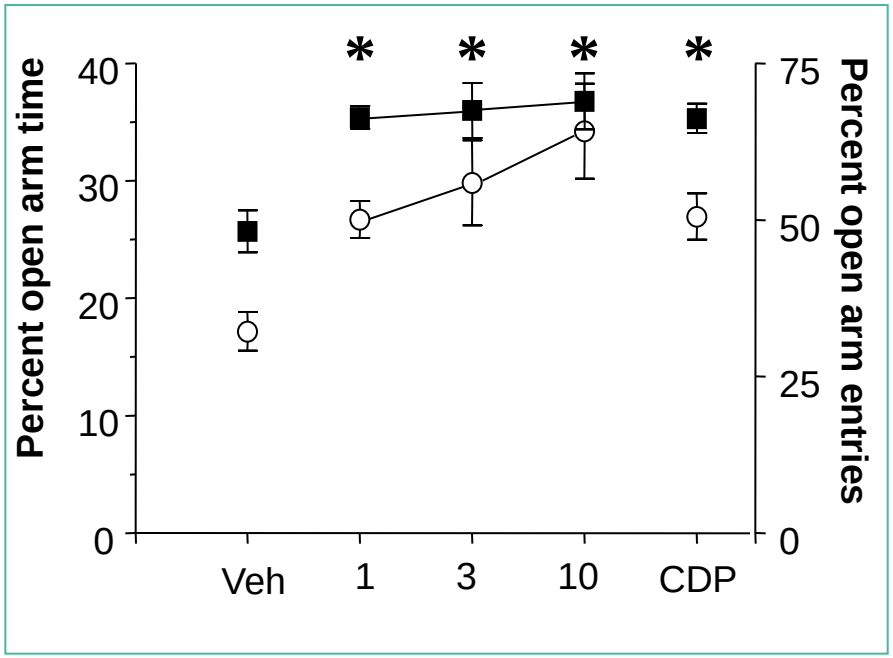
Elevated plus maze - unconditioned anxiety



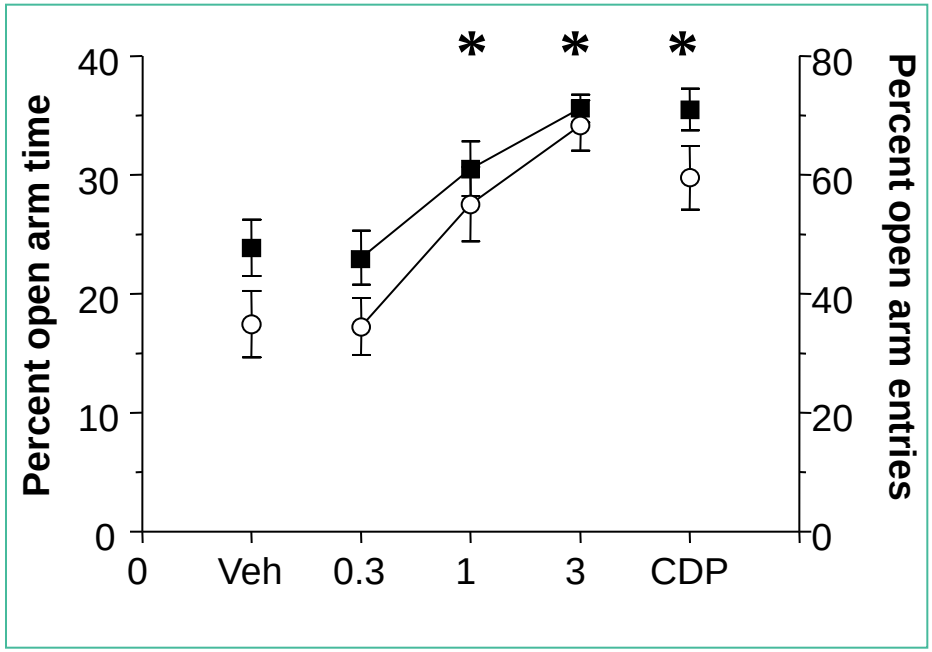
- 5 minute trial
- Rats spend typically spend <1 min exploring the open arms

Subtype selective compounds are anxiolytic in the elevated plus maze

L-838417

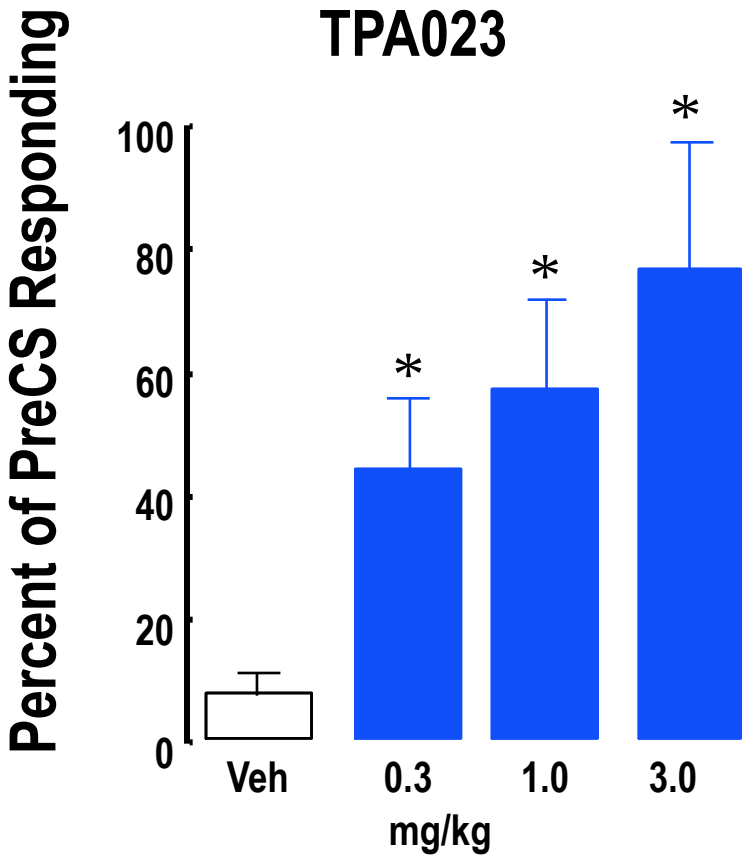


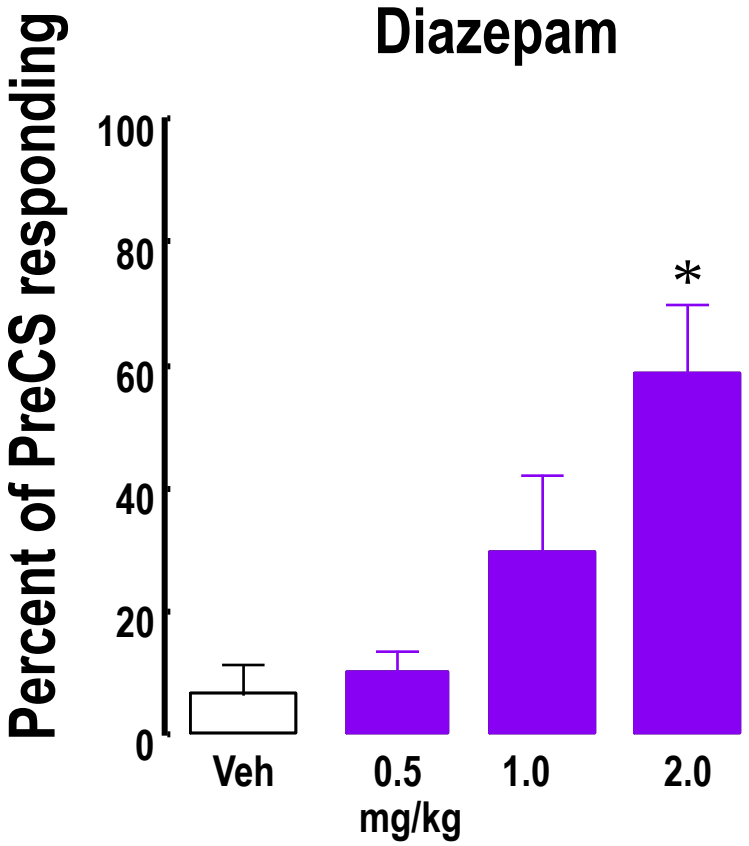
TPA 023



■ Percent open arm entries ○ Percent open arm time

TPA023 is anxiolytic in primate

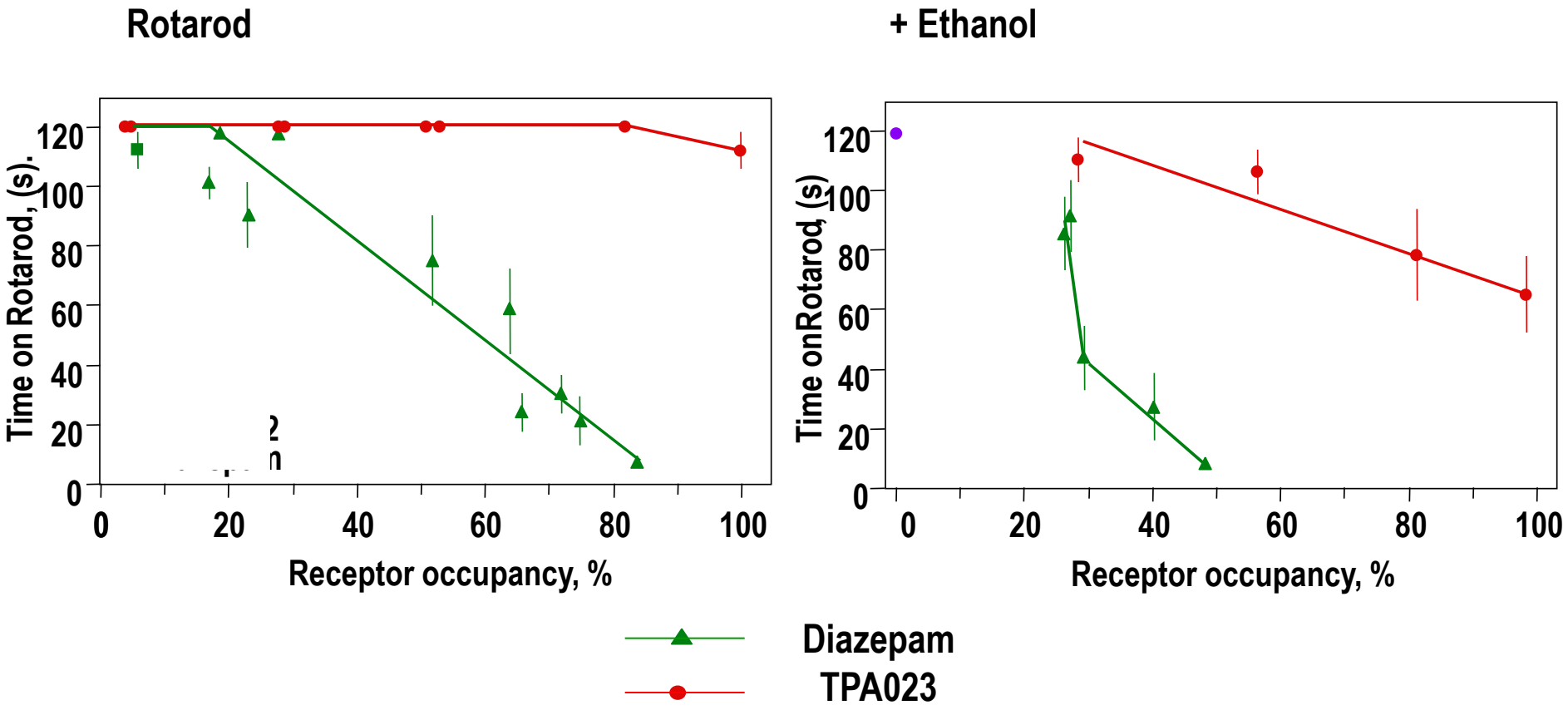




Route = PO squirrel monkey
Pre-treatment = 30 mins
* p< 0.05 compared to Vehicle

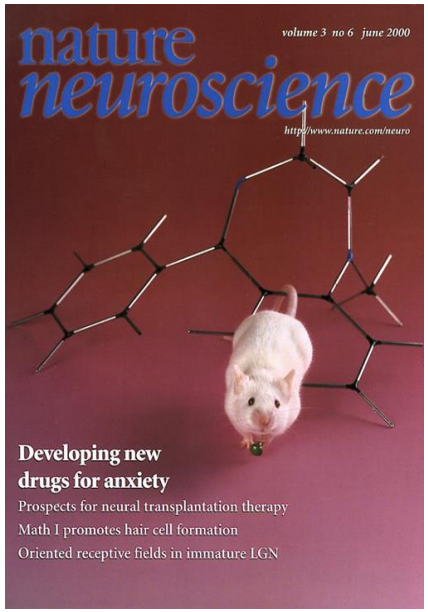
Great but what about side effects?

TPA023 has a modest interaction with ethanol



Summary of pre-clinical data

BZ Property	α1	α2/3/5
anxiolysis - exploration	-	+++
- plus maze	-	+++
- FPS	-	+++
Somnolence	+++	(+)
Ethanol potentiation	+++	+
Cognition	+	+
Dependence } James Rowlett/Nancy Ator		
Abuse potential		



Go to safety and toxicology – 1 year

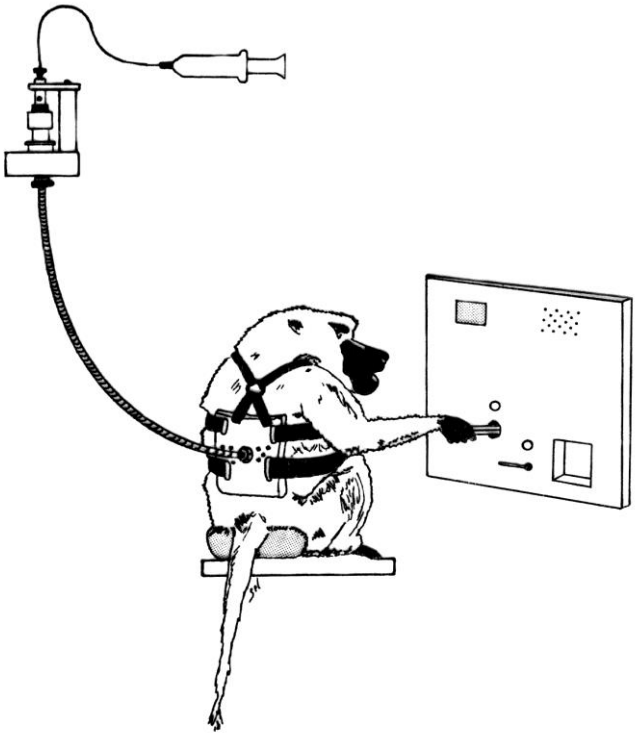
- Place your bets – stake €10M

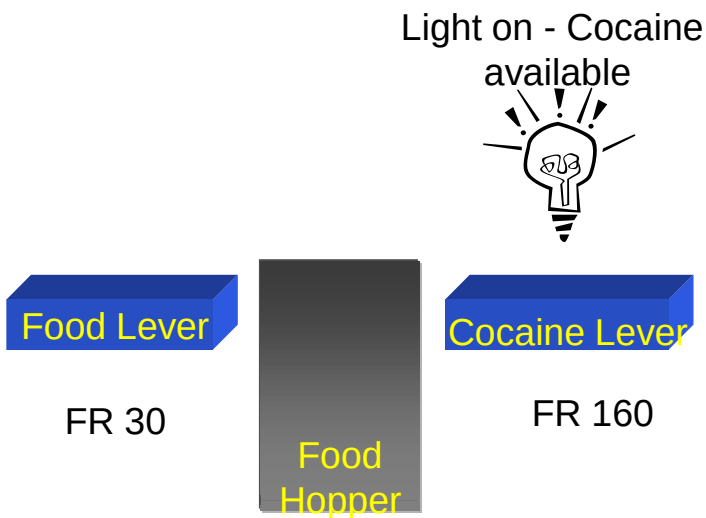
No Go – BZs have abuse potential

- FDA say does you compound have abuse potential?
- Do abuse potential study
  - Stake €2 M - 1 year development delay

- Patent life (20-4) = 16yrs
- Lost sales = €1 b.

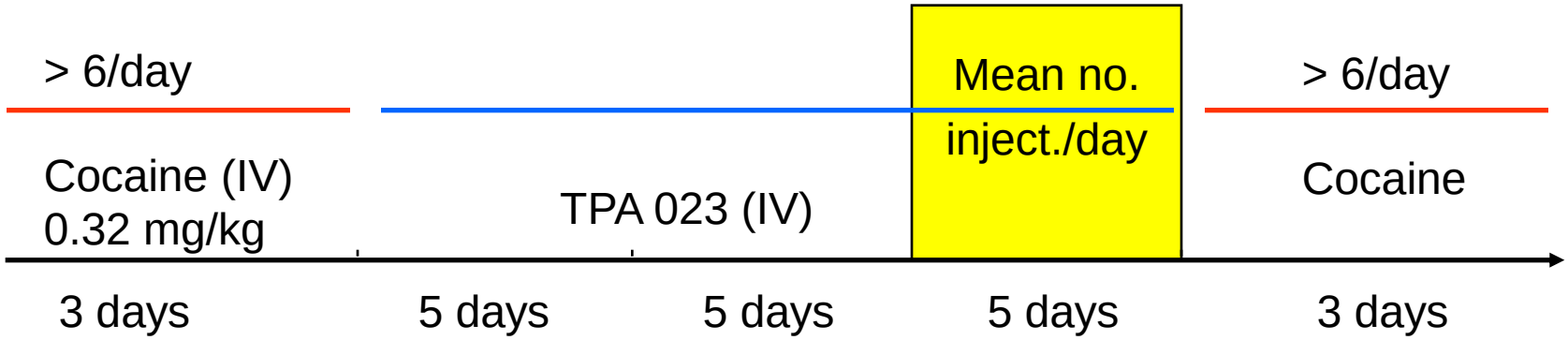
Evaluating abuse potential





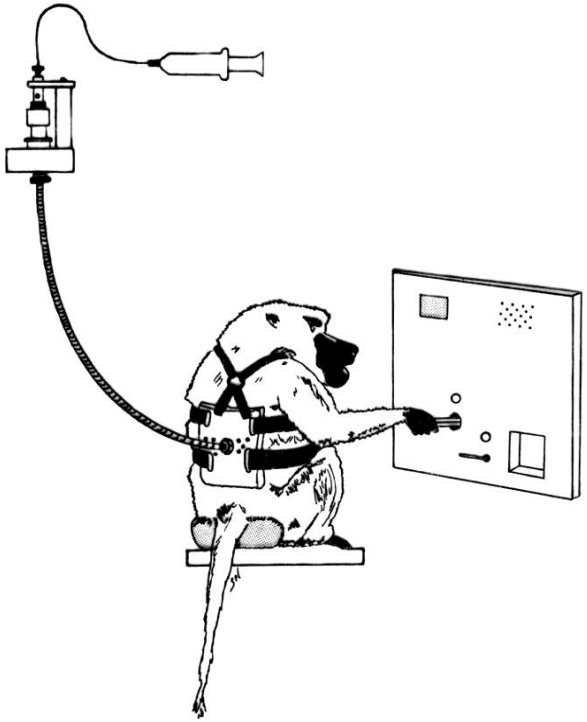
- Food available 24 hr
  - food delivered after 30 lever presses
- Cocaine (0.32 mg/kg i.v.) available every 3 hrs (max. 8 injections/day)
  - cocaine delivered after 160 level presses

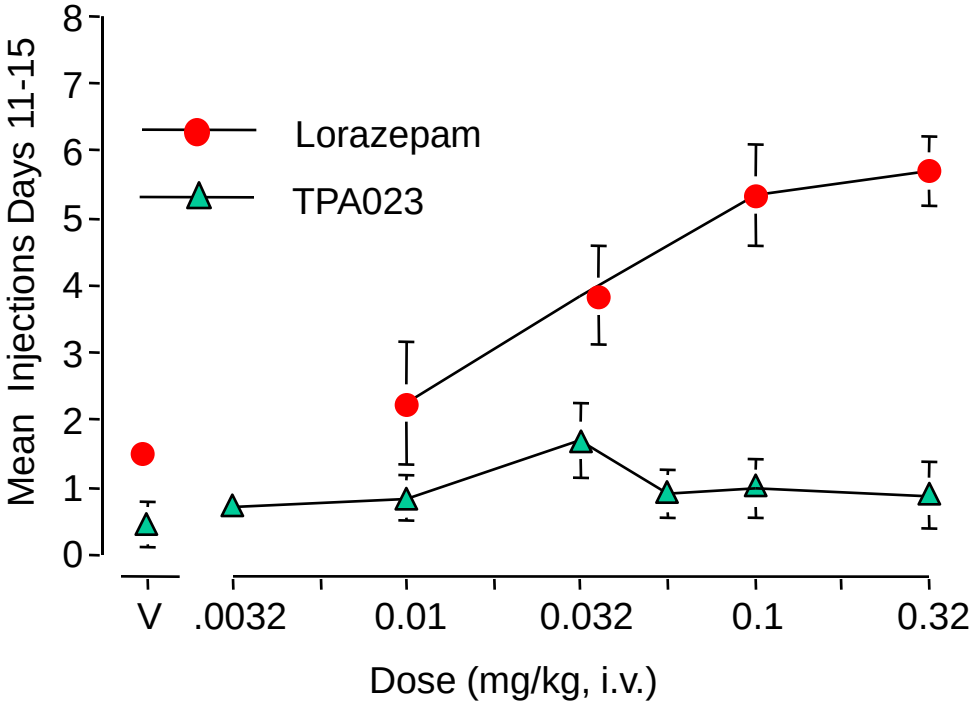
Baboon Self Administration Experimental DesignDesign



- Baboons cycle between cocaine and drug/vehicle
- Results: mean number of injections per day during the final 5 days

TPA023 - Lack of abuse potential





- TPA 023 has no abuse potential in baboons

Data from Nancy Ator, Johns Hopkins Univ., Baltimore

No abuse potential in baboon!

- Place your bets
  - Stake €10 M - 1 year safety study in you male adults

No abuse potential

- Place your bets
  - Stake €10 M - 1 safety study in you male adults

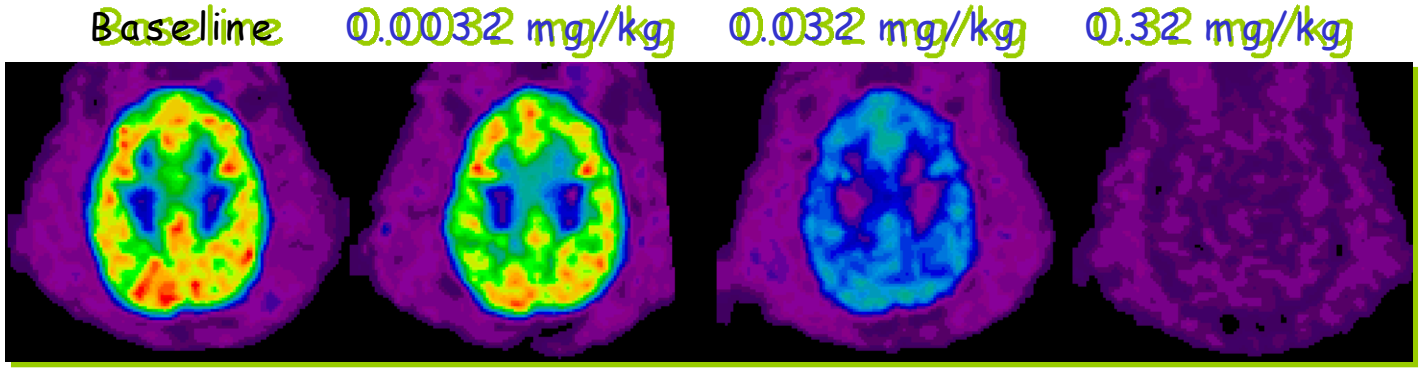
- Hold on - Does compound actually get into baboon brain and occupy receptors?

No abuse potential

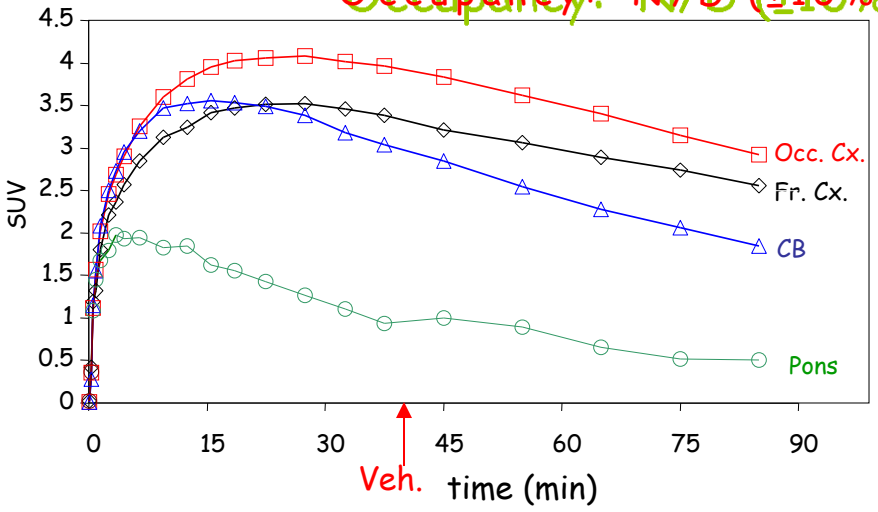
- Place your bets
  - Stake €10 M - 1 safety study in you male adults

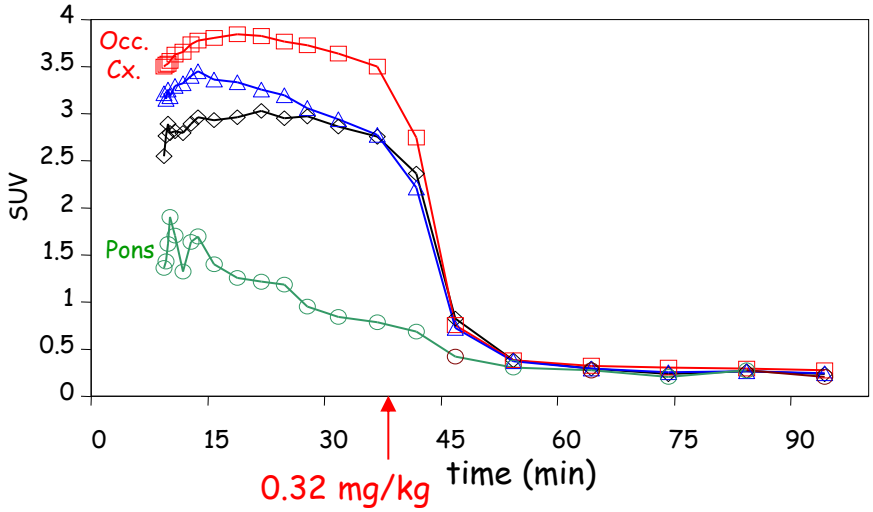
- Does compound actually get into baboon brain and occupy receptors?
- Conduct baboon PET study – 1 year delay cost - €3M

Baboon PET Studies – TPA023



Occupancy: N/D (±10%) 74% 100%

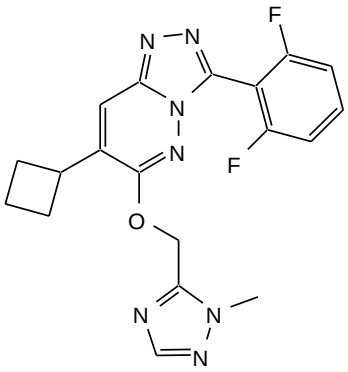


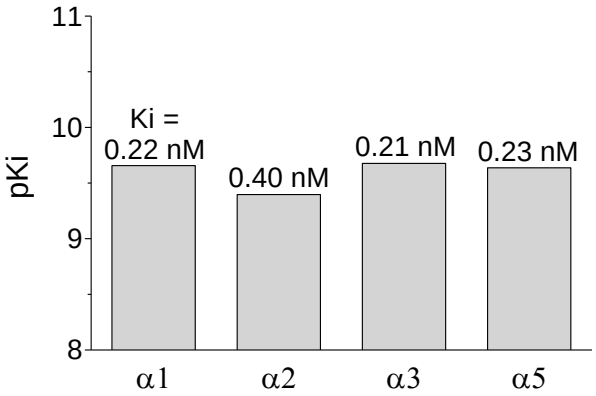


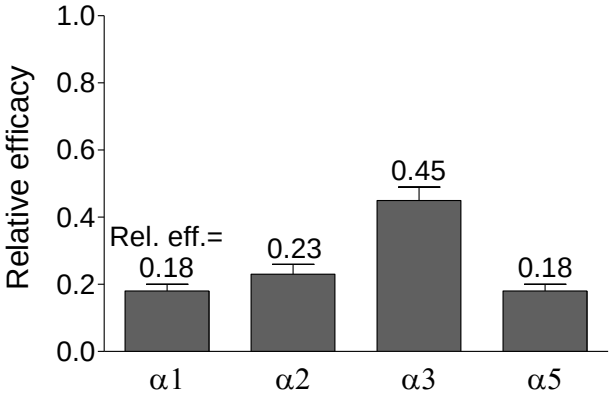
- at full receptor occupancy (0.32 mg/kg) TPA023 has no abuse potential

R. Hargreaves, MRL, West Point, PA

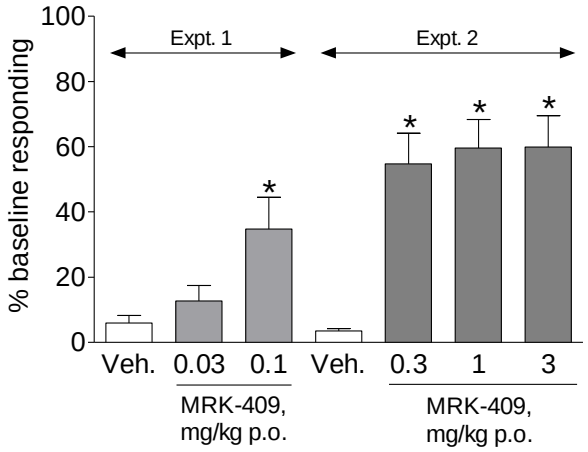
MRK-409 (MK-0343) Non-sedating anxiolytic in preclinical species



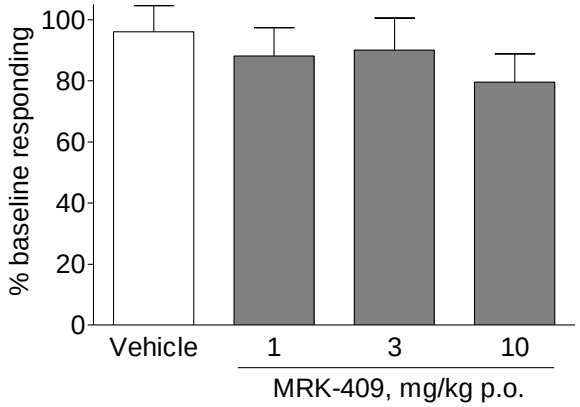




A. Anxiolysis - CER



B. Sedation - Lever-pressing

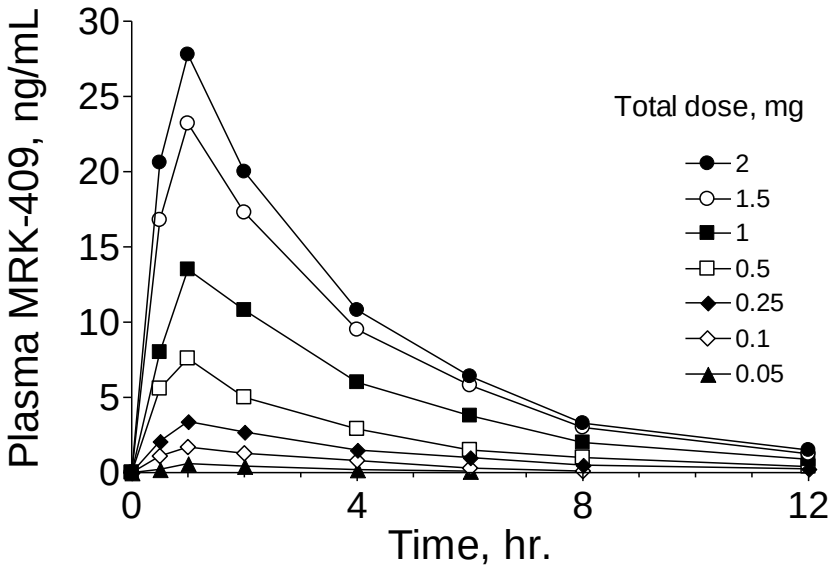


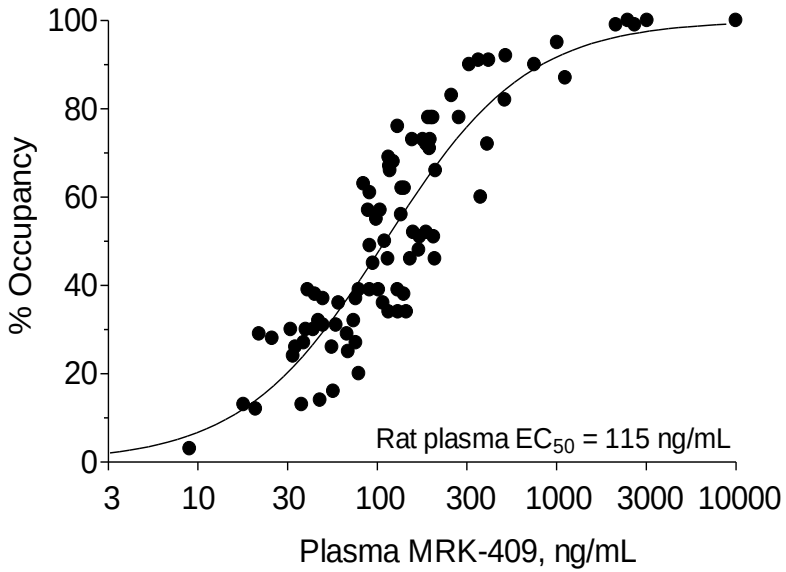
Conduct clinical study?

- Place your bets
  - Stake €10 M - 1 year safety study in you male adults

MRK-409 (MK-0343) induced sedation at very low dose

- Phase I maximum tolerated single dose = 1 mg
- Dose-limiting adverse events (1.5 and 2 mg) = somnolence





- Plasma Cmax for sedation = 20-30 ng/mL mg
  - Based on rat plasma-occupancy relationship 20-30 ng/mL = low occupancy
- What is the human plasma-occupancy relationship?

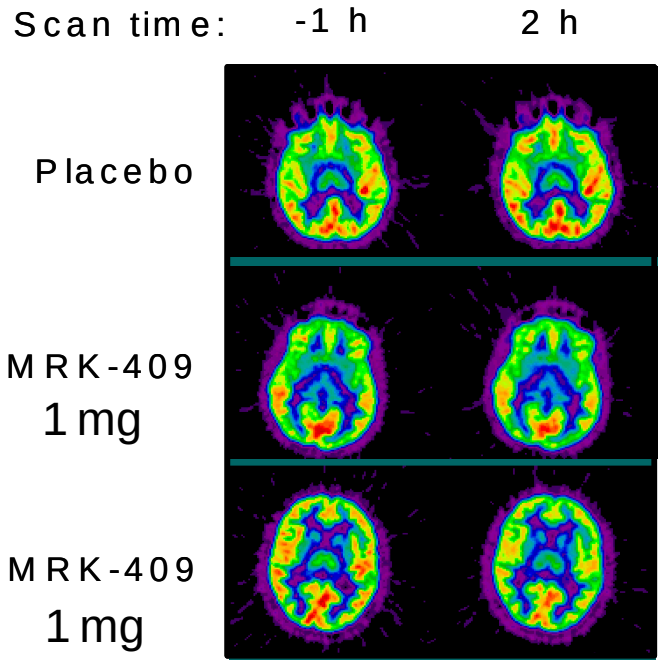
No abuse potential

- Place your bets (stake so far = €53 M)
  - Stake €5 M - 1 year PET study in you male adults

- At what receptor occupancy does sedation occur?

MRK-409 (MK-0343) induced sedation at very low receptor occupancy

- [^{11}C]flumazenil PET studies showed occupancy at 1 mg <10%
- Sedation/somnolence occurs at low levels of occupancy
  - No margin between sedation and potential anxiolysis



- Development of MRK-409 halted – Start again?

Conclusions

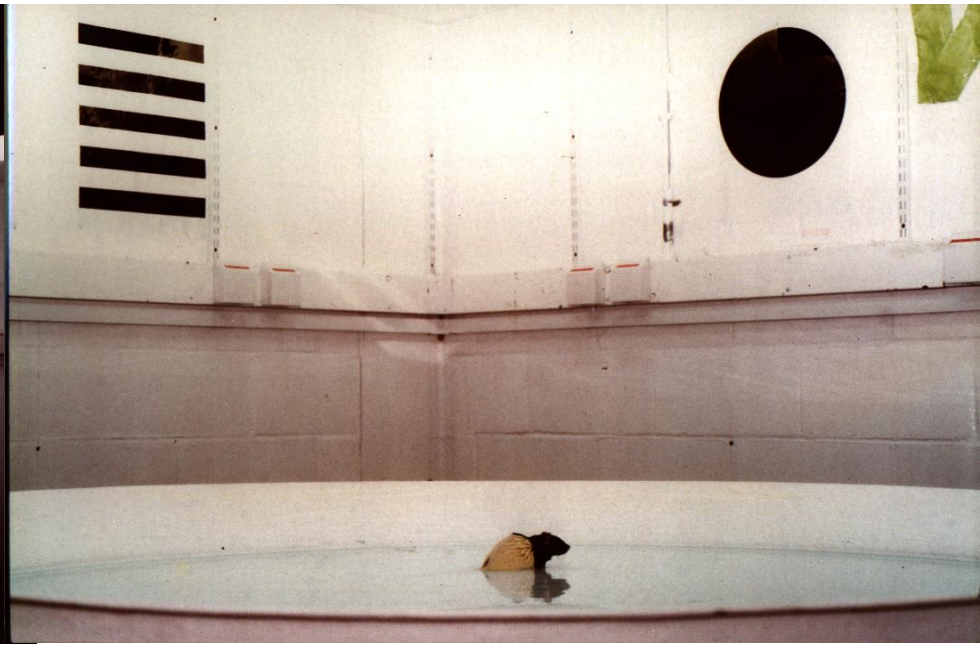
- Even the best characterised animal models do not predict effects in humans
- Path forward is in the clinic from Bed to Bench
  - patient back to animal – probably
- Mantra – ‘Fail early, fail cheap’
  - 90% No/Go, early decisions are cost effective
  - We failed cheap despite €50M+ costs
  - Phase 3 failure costs €300M+ costs
    - NK-1, bitopertin
  - Experimental Medicine solutions

Alzheimer’s disease

- Alzheimer’s disease the most common cause of dementia affects 4 million US citizens
  - As more and more Americans live longer, the number affected by Alzheimer's disease will continue to grow unless a cure or effective prevention is discovered.
- Current therapies (cholinesterase inhibitors) have significant limitations
  - Side-effects including nausea, diarrhoea, vomiting
  - Little or no effect on disease progression
- Need for an well tolerated treatment that slows or halts disease progression
- Registration trials require large numbers of patients
- Potential for Experimental Medicine studies to select best compound(s) for late stage trials

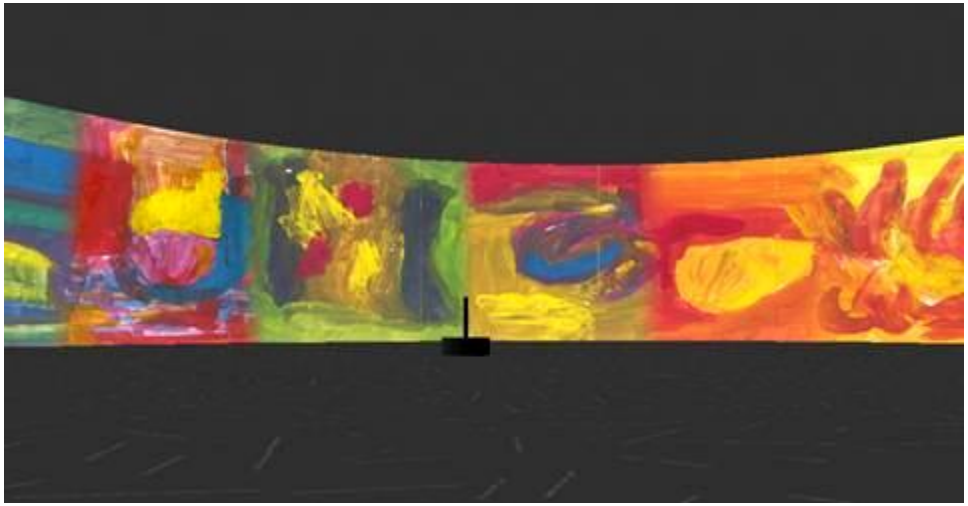
Human spatial memory & fMRI

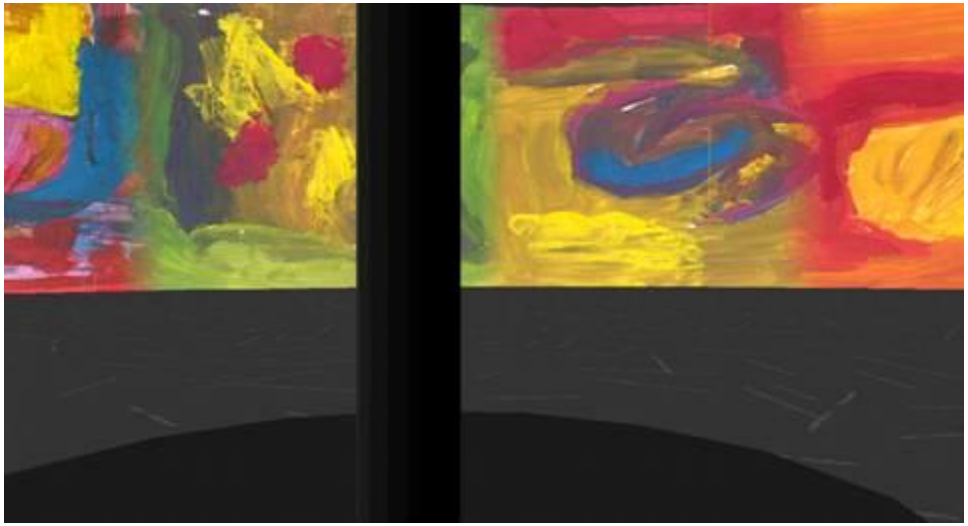
- Develop spatial learning and memory paradigms that engage hippocampal processing
  - Image participants to ensure hippocampal activation during task
  - Test participants during encoding and recall to determine differential activation
  - Determine effects of age on performance
  - Determine effects of drugs on performance
  - Optimise fMRI methods for clinical trials
- Virtual reality task developed and validated
  - Arena maze (human analogue of Morris water maze)
    - Easy to administer, flexible designs, validated with scopolamine and healthy elderly participants



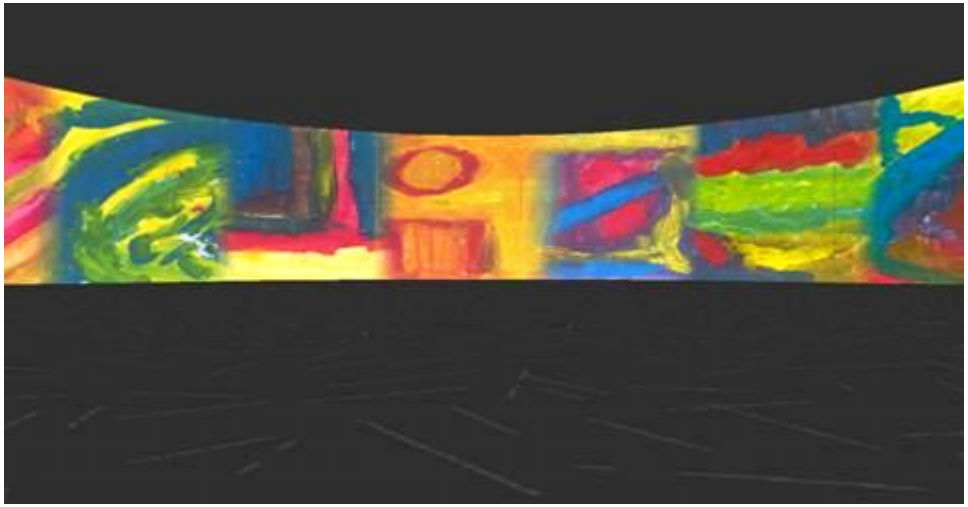
- Rats are placed in a 2m diameter pool containing a hidden platform
- Rat finds platform and notes position in relation to a number of visual cues
- Time taken to swim to platform is recorded over a series of trials (= learning)
- Platform removed and time spent in platform quadrant is recorded (probe trial = memory)

Arena pole paradigm: encoding





Arena pole paradigm: retrieval



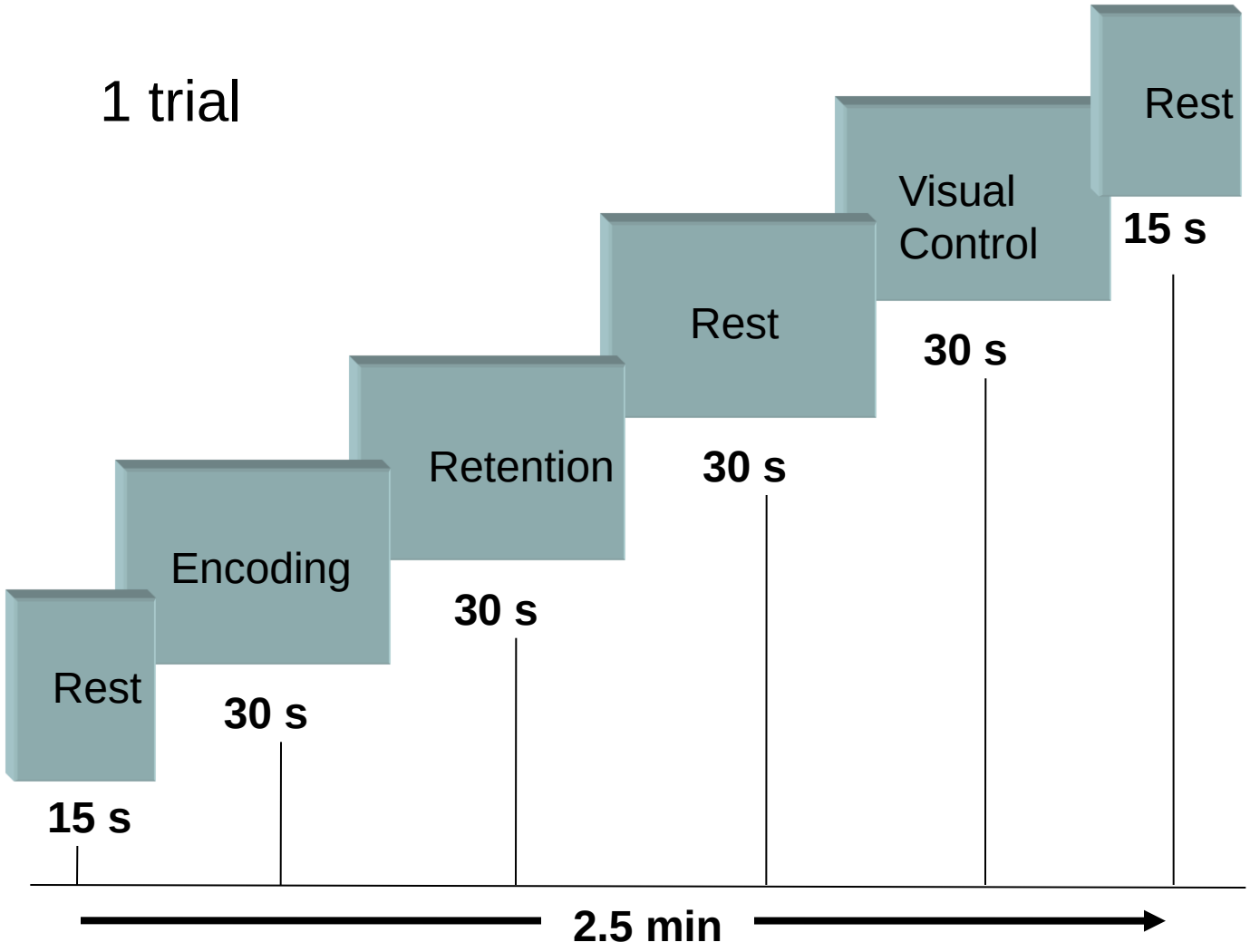
Play M`ovie

Study 2: Aging effects

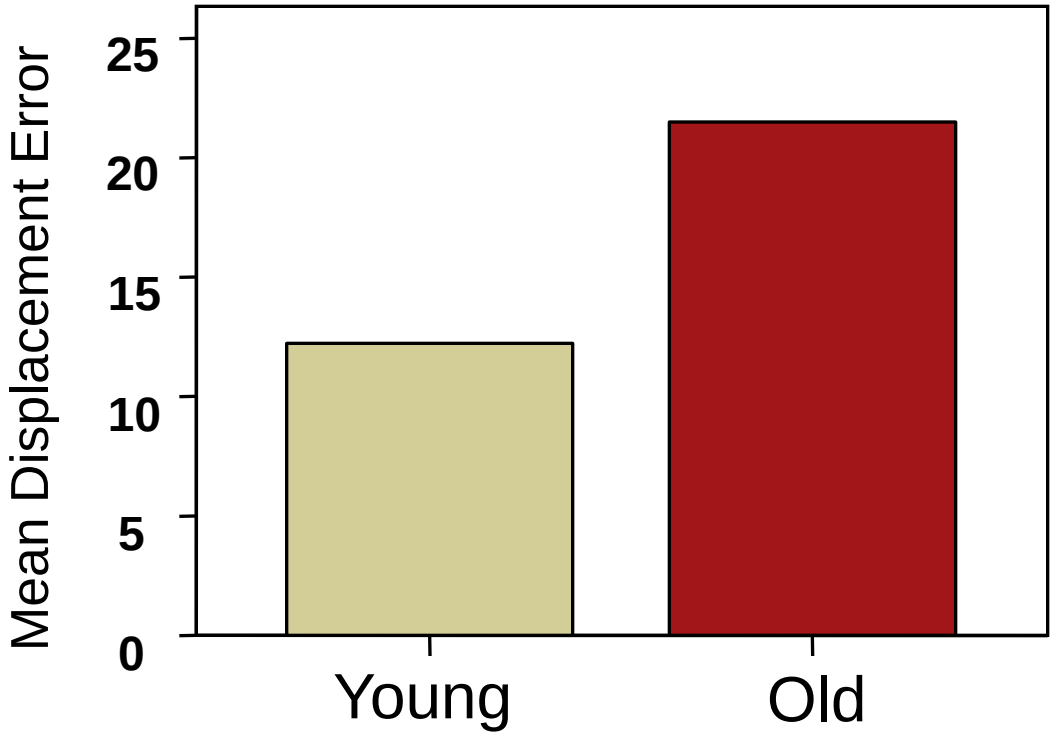
Procedures

- Groups
  - Young healthy adults (Mean age = 24 years
    age range = 20-26, n=11)
  - Elderly healthy adults (Mean age = 72 years
    age range = 64-79, n =9)
- Young participants trained on 18 trials to criterion
- Older participants trained on 36 trials to criterion

fMRI Design


1 trial
Rest
Encoding
Retention
Rest
Visual Control
Rest
15 s
30 s
30 s
30 s
30 s
15 s
2.5 min

Behavioural Results: Young vs Old



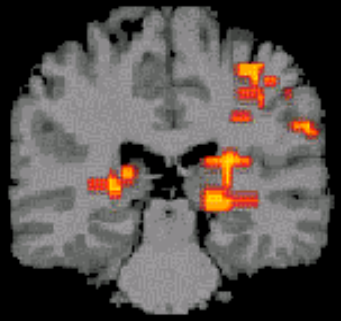
Older participants performed significantly worse across three experimental blocks of trials (each block = 6 trials, $t_{17} = -3.542$, $p = .003$]

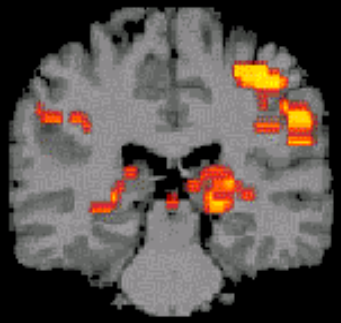
Reduced Hippocampal Activation in Elderly Subjects

Encoding

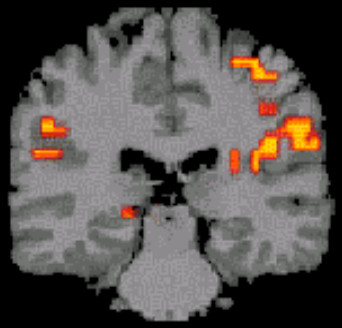
Retrieval

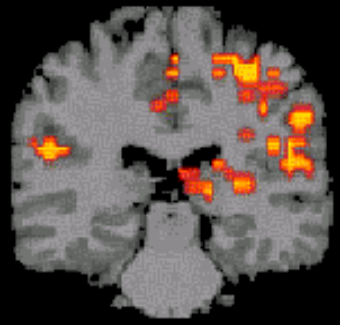
Study 2 Young Male (20-26 years old)





Study 2 Elderly Male (65-79 years old)



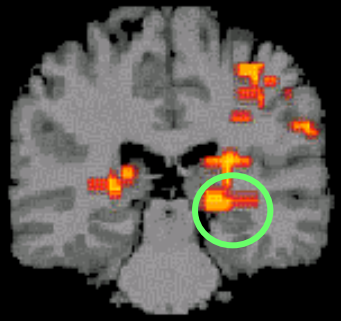


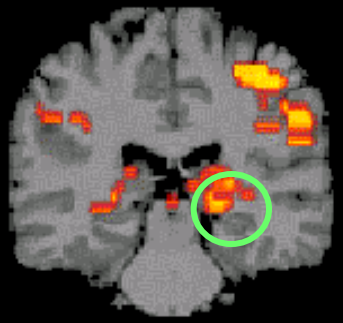
Reduced Hippocampal Activation in Elderly Subjects

Encoding

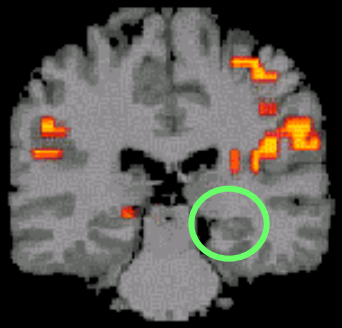
Retrieval

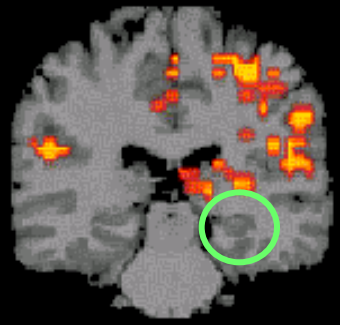
Study 2 Young Male
(20-26 years old)





Study 2 Elderly Male
(65-79 years old)



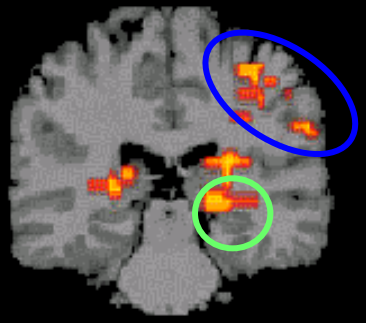


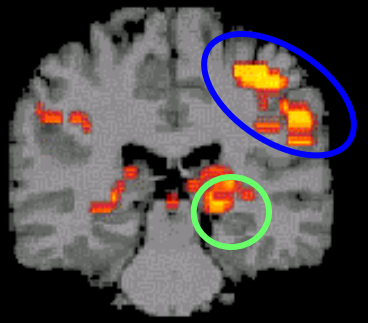
Reduced Hippocampal Activation in Elderly Subjects

Encoding

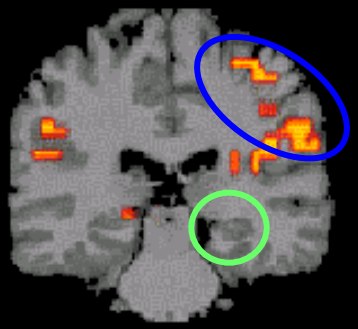
Retrieval

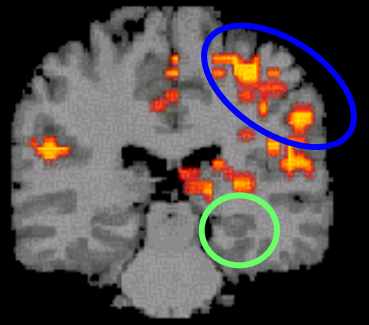
Study 2 Young Male (20-26 years old)





Study 2 Elderly Male (65-79 years old)



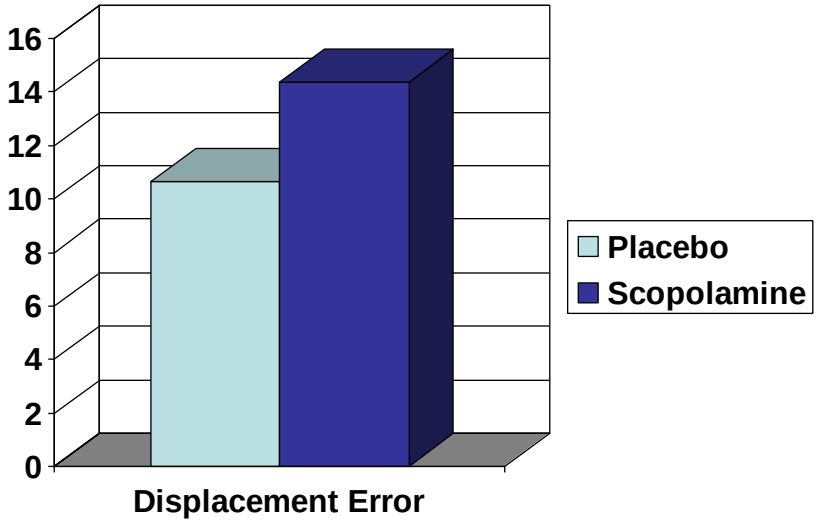


Effects of scopolamine on behavioural performance and fMRI measures

- 20 young participants
- Scopolamine 0.4 mg vs placebo
  - Cross-over study
- fMRI measurement
  - 3-Tesla MRI

Antonova E, at l. J Psychopharmacol. 2011, 25:1256-65.

Behavioural results: scopolamine vs placebo

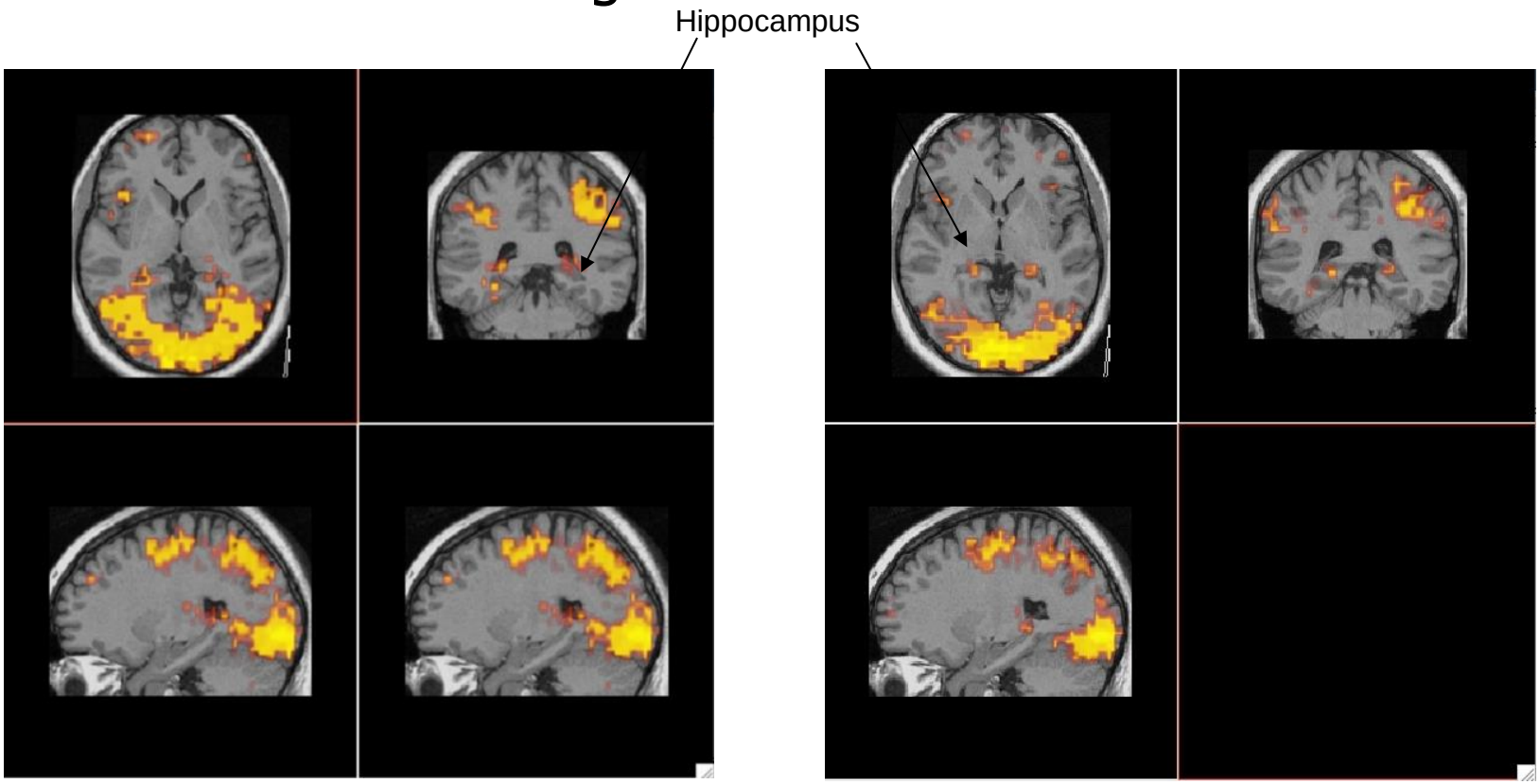


- Scopolamine significantly impaired performance
  - Placebo group: Mean displacement error = 10.67, SD = 4.22
  - Scopolamine group: Mean displacement error = 14.39, SD = 7.37

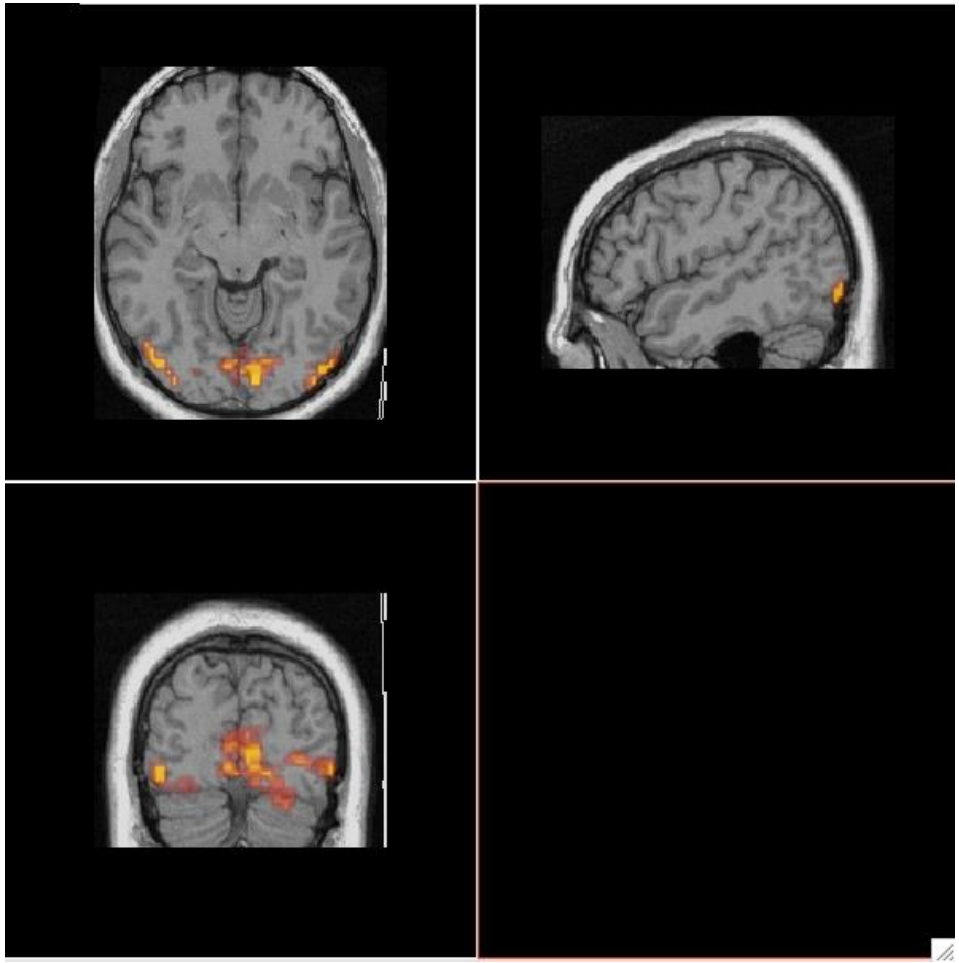
Hippocampal activation in placebo condition

Placebo -Encoding

Placebo - Retrieval



Reduced hippocampal activation induced by scopolamine

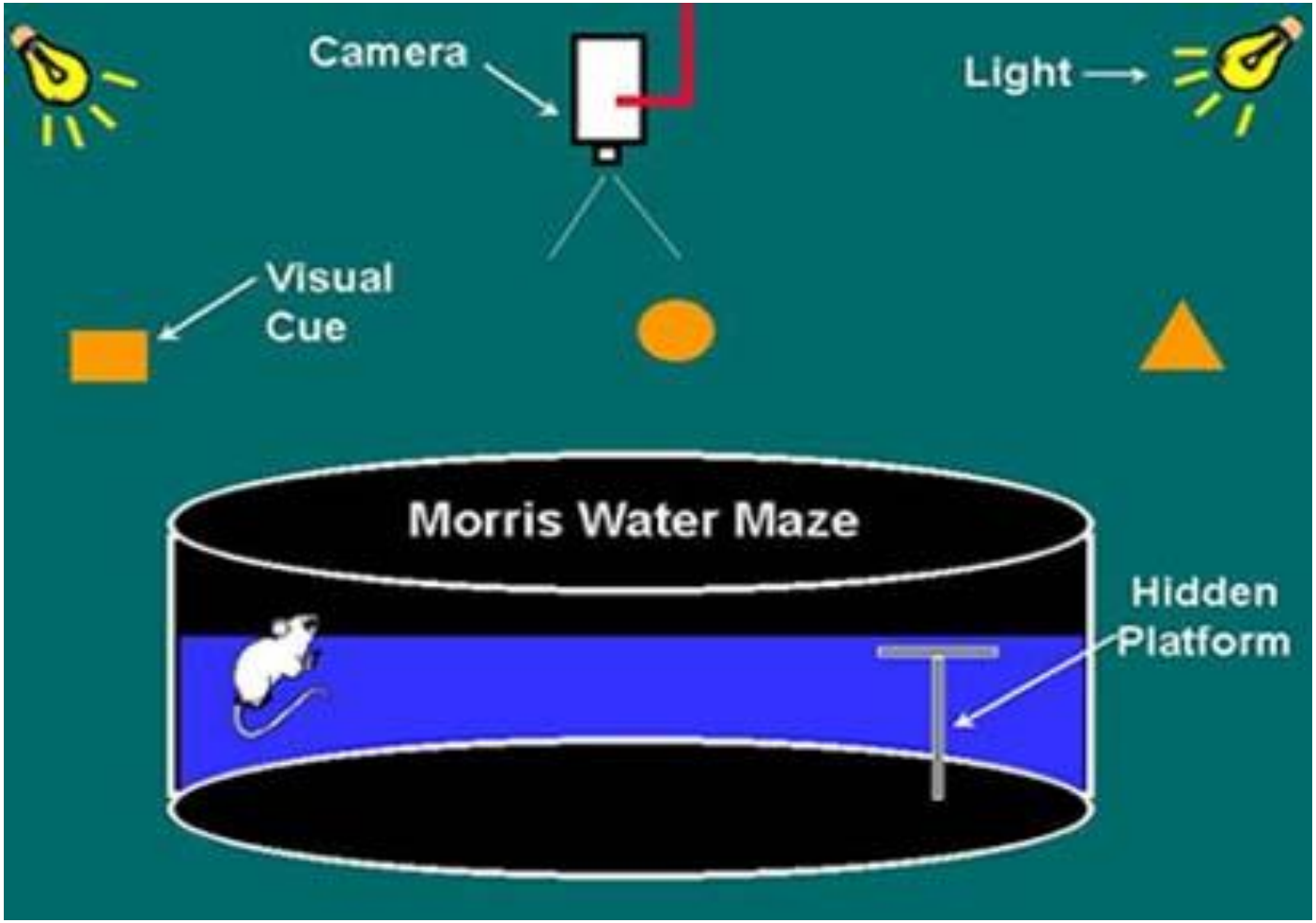


Placebo

>

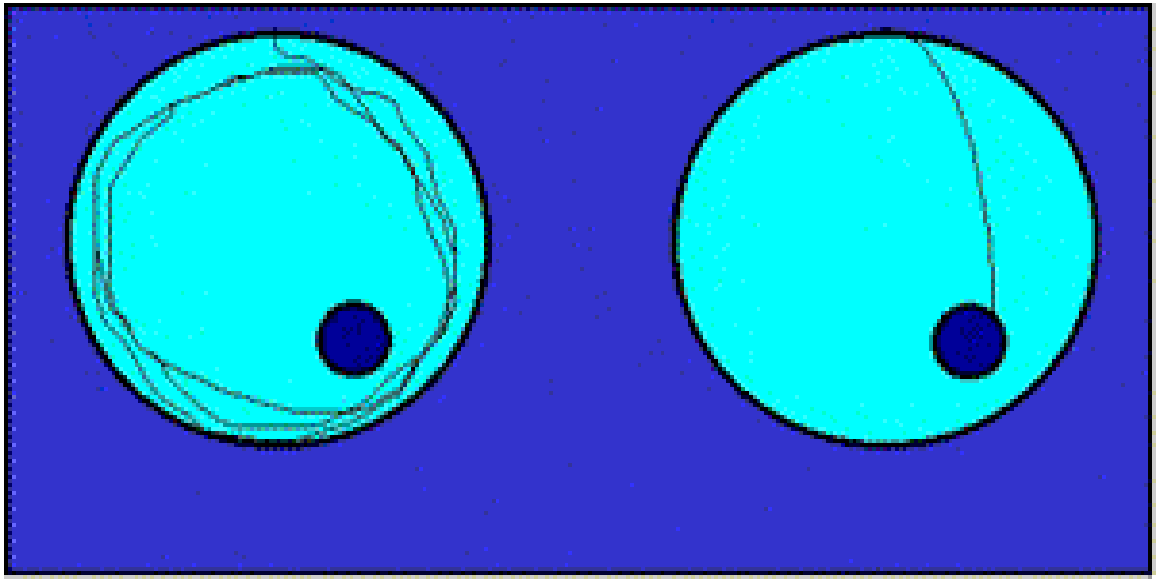
Scopolamine

Morris Water Maze Model of Cognition

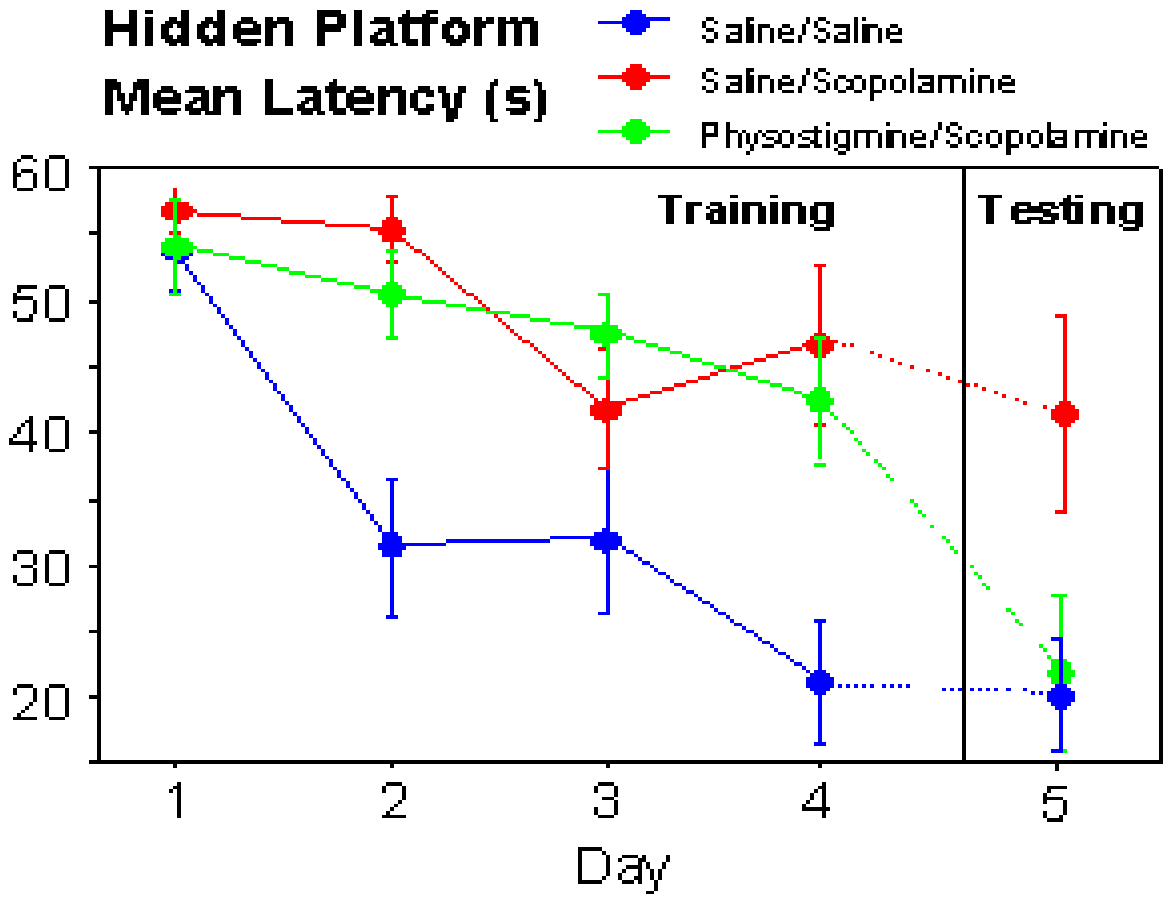


Morris Water Maze

Path-length at the beginning and at the end of the training period



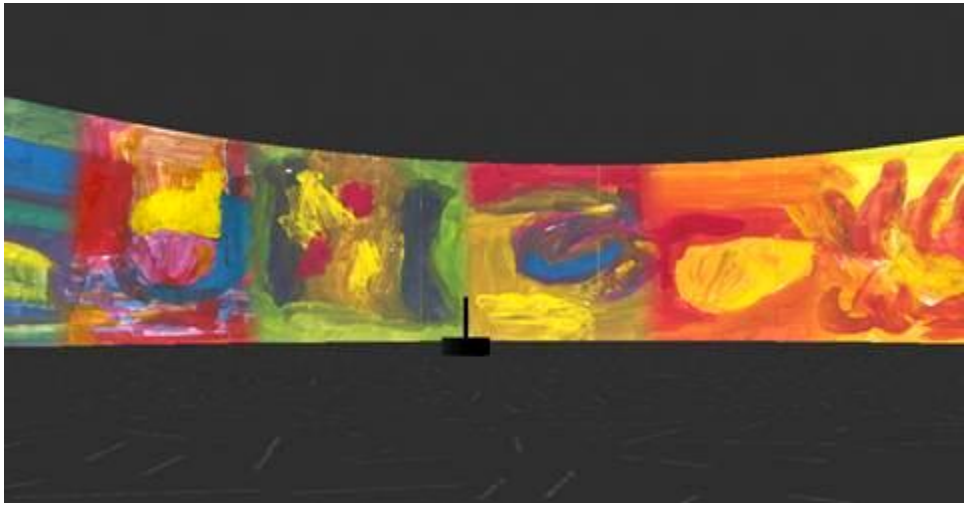
Morris Water Maze: Scopolamine

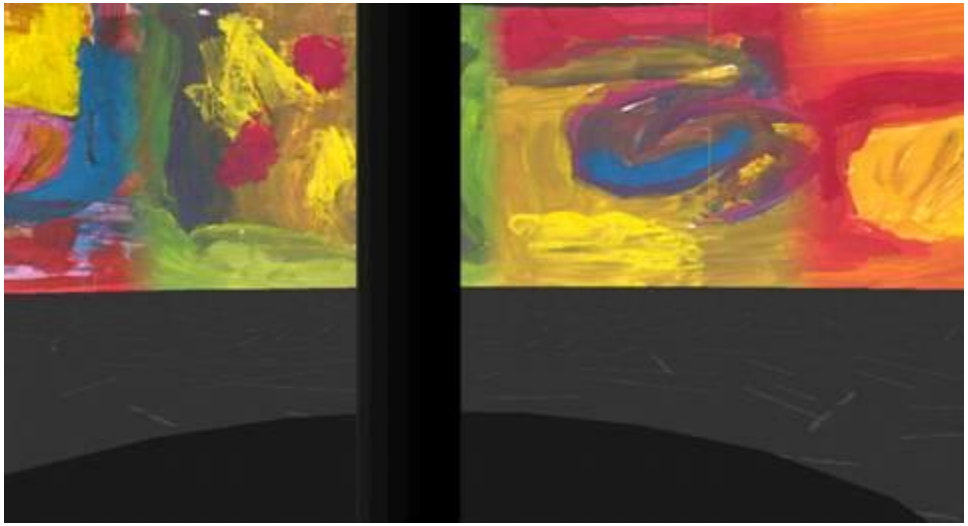


Spatial Memory Flat Mapping & fMRI

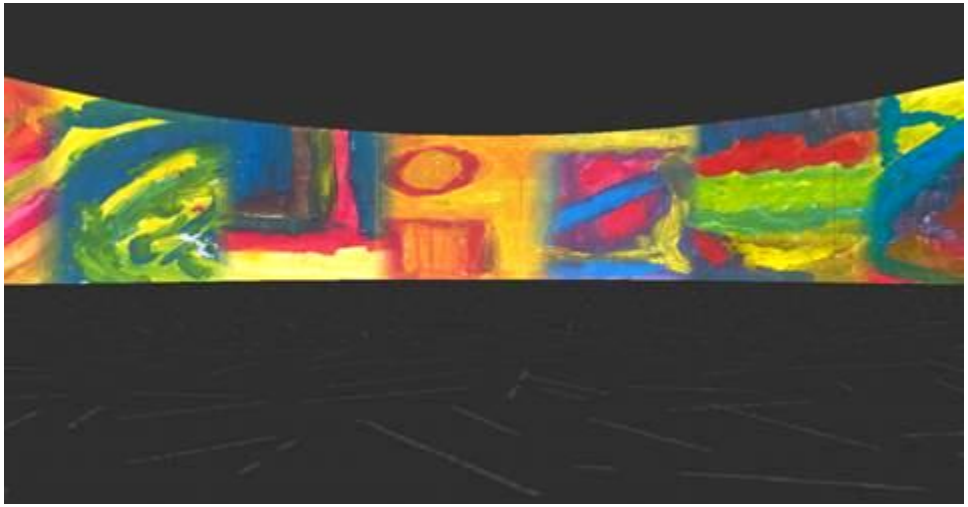
- Develop spatial learning/memory paradigms that engage hippocampal processing
- Image subjects to ensure hippocampal activation during task
- Test subjects during encoding and recall to determine differential activation
- Determine effects of age on performance
- Determine effects of drugs on performance
- Optimise fMRI methods for clinical trials

Arena Pole Paradigm: Encoding





Arena Pole Paradigm: Retrieval



Arena Pole Paradigm: Visual Control Task

Play Movie

Future Developments

- Software validated with young healthy volunteers given placebo, scopolamine and butylscopolamine
- Flat mapping development parallels testing

  Flat mapping.ppt
- Spatial learning in a natural environment (e.g. shopping trip)