

Pitfalls and prospects for cognitive assays in preclinical research

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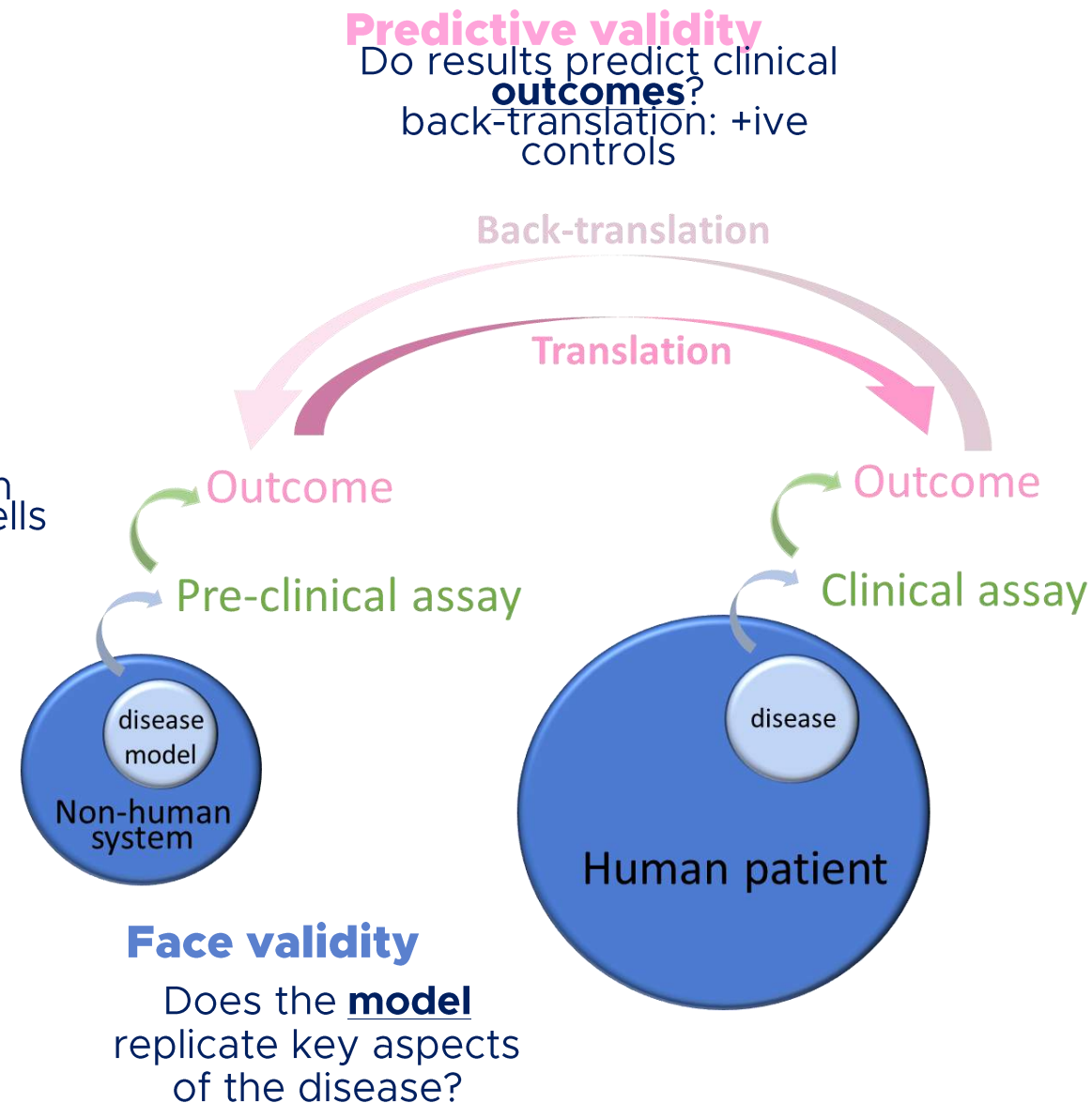
What do we mean by translation?

Replication of pre-clinical data from academic to industry labs depends on “good science”

- Standardised protocols
- Avoiding bias in reporting
- Properly powering studies
- ...etc...

Industry is primarily concerned with translation to clinical results

Construct validity
Does the assay detect changes in disease-relevant cells or circuits?



The right test for the right domain

...construct validity...

- **Not definitive nor exhaustive!**

- ✱ **Attention (visual cortex, lateral PFC, cholinergic system)**

- 5-choice serial reaction time
- Sustained Attention Task

- ✱ **Working memory (medial PFC, HIPP)**

- Delayed non-match to sample/place
- Y-maze (spontaneous alternation)

- ✱ **Recognition memory (MTC/HIPP, perirhinal cortex, PFC, more)**

- Novel object recognition

- ✱ **Spatial / “episodic-like” memory (MTC/HIPP)**

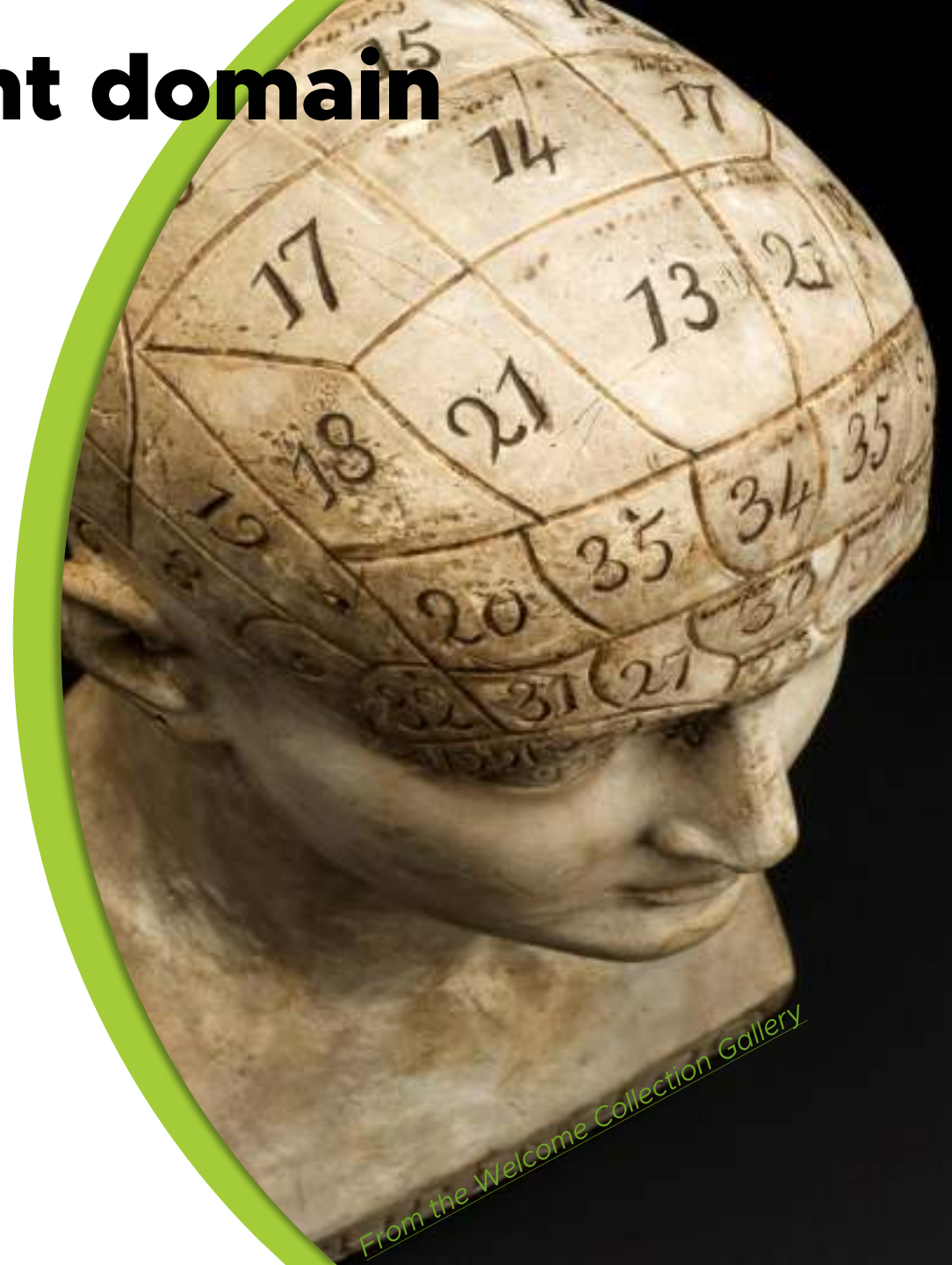
- Morris Water Maze
- Radial Arm Maze
- T-maze forced alternation
- Contextual fear conditioning (+amygdala)

- ✱ **Cognitive flexibility (PFC, B.ganglia, ACC, more)**

- Attentional set shifting
- Reversal learning

- ✱ **Inhibitory Control (inferior frontal cortex)**

- Go/No-go tasks



From the Wellcome Collection Gallery

Pitfall#1: Forget that cognition matters

... In an age of proteomics, AI, digital health etc!

* Cognition is often the primary endpoint in clinical trials

- Example: ADAS-Cog, a gold-standard test for Alzheimer's symptoms
- Failure to improve = failure of the trial
- **regardless** of whether (for example) your treatment successfully clears amyloid!

* Cognitive assays provide a more complete, system-wide picture of treatment effects

- Adverse effects can also be detected
- E.g. termination of recent clinical trials for BACE-inhibitors targeting AD - due to a **worsening** of patient cognition scores.
- Nevertheless, reviews profiling new drugs still often fail to consider any cognition endpoints (see at right)

Alzheimer Disease Assessment Scale— Cognitive Subscale (ADAS-cog) 11-Item	
	Score range
Memory and new learning	0 - 35
Word recall (mean number of words not recalled)	0 - 10
Orientation (one point for each incorrect response)	0 - 8
Word recognition (mean number of incorrect responses)	0 - 12
Remembering test instructions	0 - 5
Language	0 - 25
Commands	0 - 5
Spoken language ability	0 - 5
Naming objects/fingers	0 - 5
Word-finding difficulty	0 - 5
Comprehension	0 - 5
Praxis	0 - 10
Constructional praxis	0 - 5
Ideational praxis	0 - 5
Total	0 - 70

Increasing score indicates worsening of cognition
Rosen WG, et al.

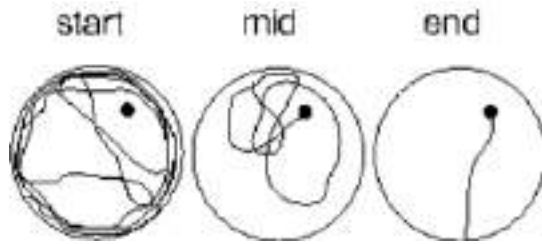


REVIEW ARTICLE | Free Access

The β -secretase (BACE) inhibitor NB-360 in preclinical models:
From amyloid- β reduction to downstream disease-relevant
effects

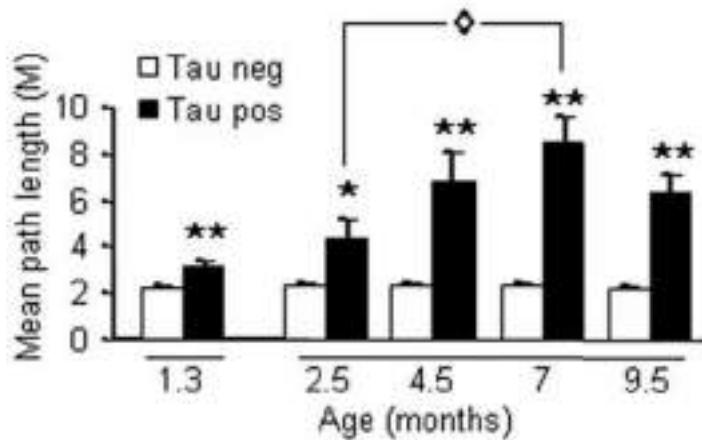
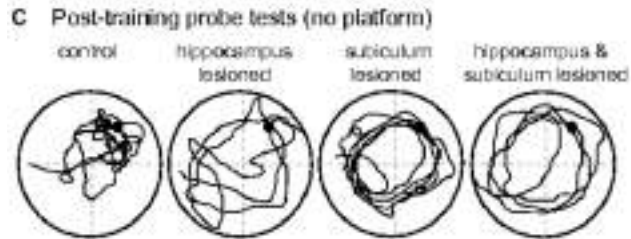
Pitfall#2: Don't understand your assay

... e.g. very popular Morris Water Maze for spatial memory



Rat must learn to swim directly to a hidden platform from a random start-position

http://www.scholarpedia.org/article/Morris_water_maze



Tg4510 mouse model of tauopathy
Ramsden et al, 2005

Performance is impaired in:

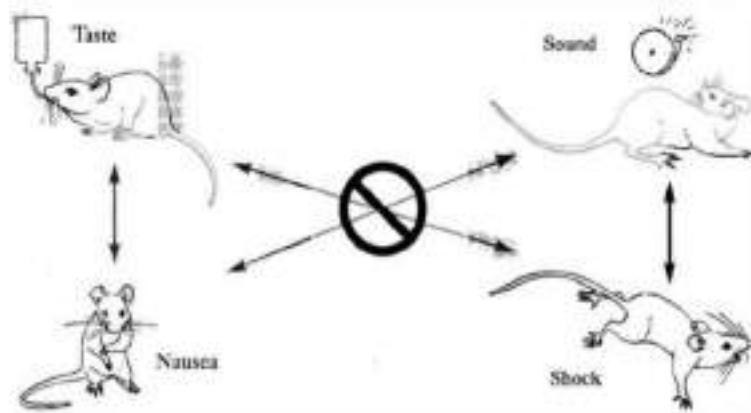
- **Hippocampal** lesioned animals (construct)
- **Pharmacological** and **transgenic** models of Alzheimer's Disease

However...

- **Aversive** – hence anxiety/stress matters
 - Effects could be **anxiolytic**
- **Overtrained** animals use non-hippocampal strategies
 - Loss of construct validity
- **Motor effects can be a confound**
 - **Path-length** or probe test are better than escape latency

Pitfall#3: Don't understand your species

.... Ethological relevance



* **Garcia & Koelling, 1966**

* **Rats easily make some associations:**

- nausea with the flavour of their drinking water
- foot-shock with lights and sounds near the water

* **However, they will struggle to associate nausea with “bright noisy” water, or foot-shock with the flavour.**

- These are simply not naturally adaptive associations – they are not “wired” to make them

* **Assays ideally tap into natural behaviours**

* **Be cautious adapting cognitive assays to other species**

- Unlike rats, mice are not particularly good swimmers
 - Commonly adopt a “floater” stress response in MWM
- Excess or incorrect handling causes a lot of stress in mice
 - Use proper handling techniques
 - Allow longer habituation times
 - Automate tasks where possible



<https://www.nc3rs.org.uk/how-to-pick-up-a-mouse>

Pitfall#4: It's good, but is it affordable?

... example: Attentional Set-Shifting (ID/ED) Task

A gold standard test of cognitive flexibility

- Highly translational, ethological

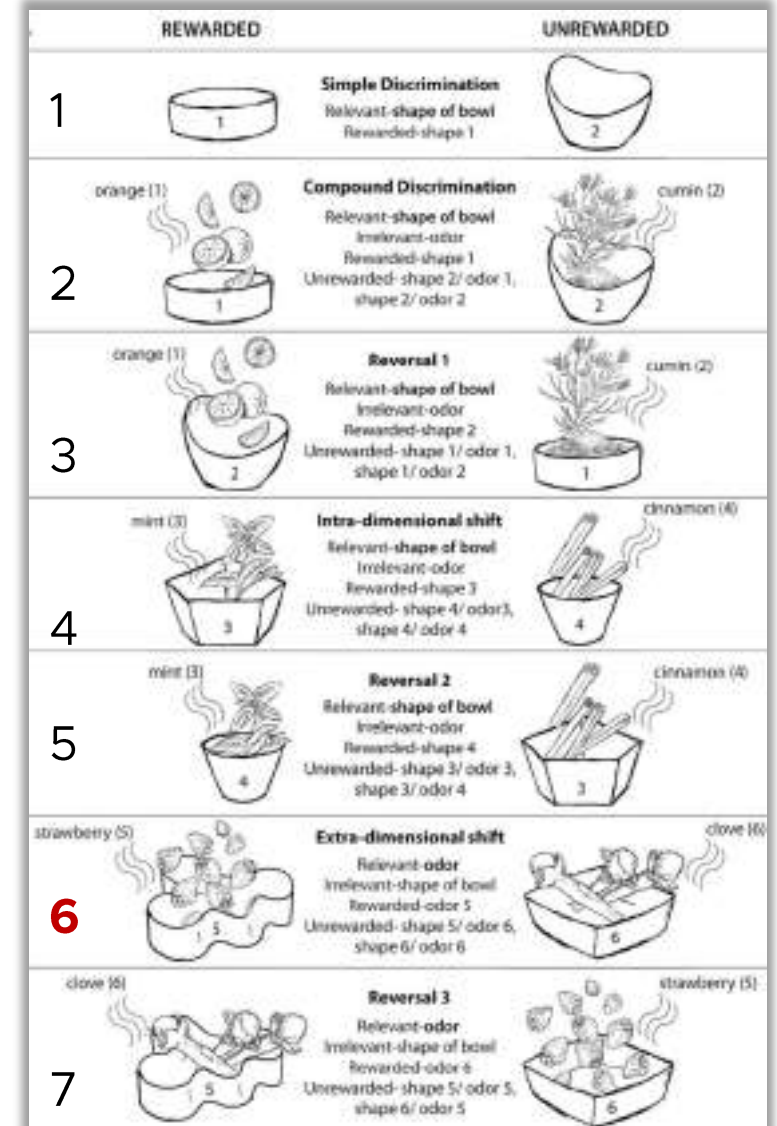
However, it is very laborious to run

- Stage-6 is impaired in schizophrenia

If your intended end-user lacks the manpower or the budget, it's unlikely to be adopted

For any test, consider the labour required!

- avoid running underpowered studies





Prospects

International efforts establish cross-site reproducibility

... Academia + Lilly, Janssen, AbbVie, Pfizer, Roche, Orion, Lundbeck



IMI1 Final Project Report Public Summary

Project Acronym: NEWMEDS

Project Title: Novel Methods leading to New Medications in Depression and Schizophrenia

Grant Agreement: 115008
Project Duration: 01/09/2009 - 28/02/2015

Linking animal and clinical models of cognition

- Cognitive test battery for both mice and rats
- Harmonised protocols
- Automated tasks where possible (e.g. touchscreen)

MAM-E17 rats:

- High level of agreement across sites

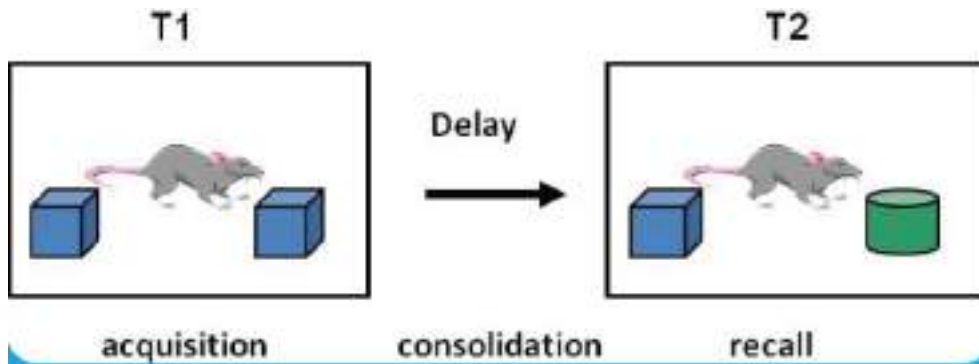
Site	PPI	Basal & PCP hyperactivity	Touchscreen VD & Reversal	Attention Learning & Memory	Neuroanatomy
AbbVie	-	↑	-	↓	↓
Lilly	-	↑	-	↓	↓
Orion	-	↑	-	↓	↓
Pfizer	N/A	↑	-	↓	N/A
Lundbeck	N/A	↑	-	N/A	N/A
Reliability	100%	100%	100%	100%	100%

The assays are good – just standardise their use!

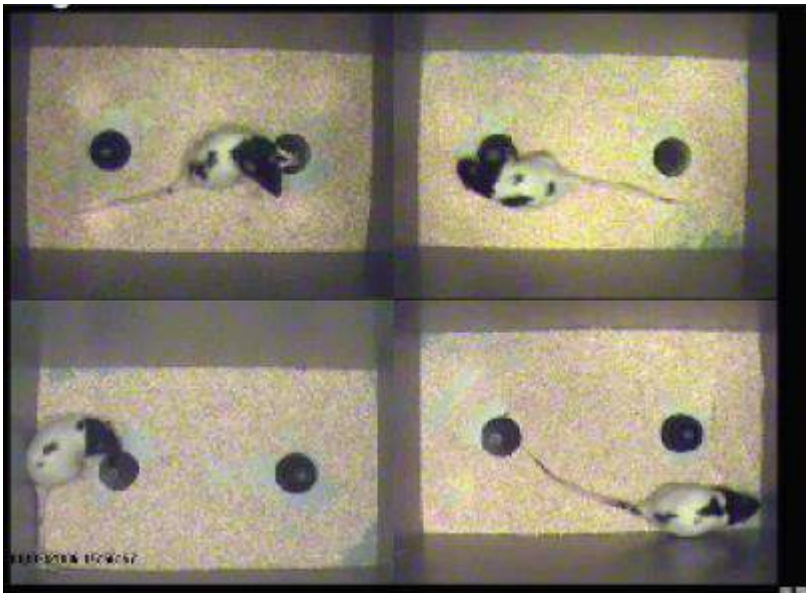
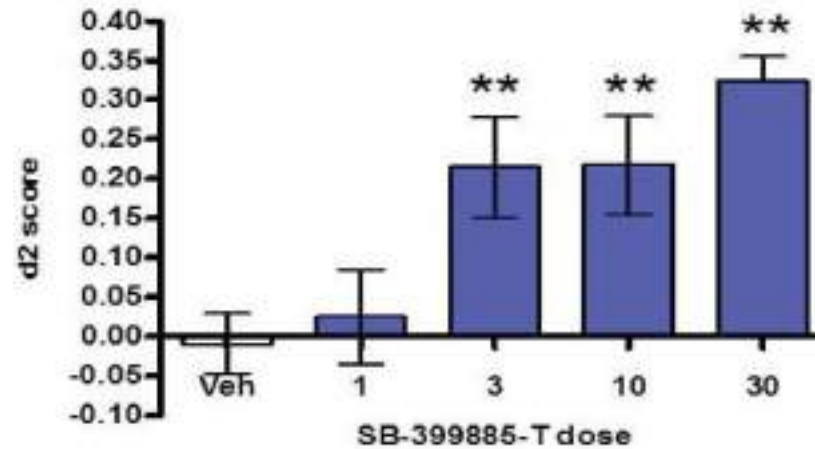
In house reproducibility is equally important

... e.g. Novel Object Recognition at Transpharmation

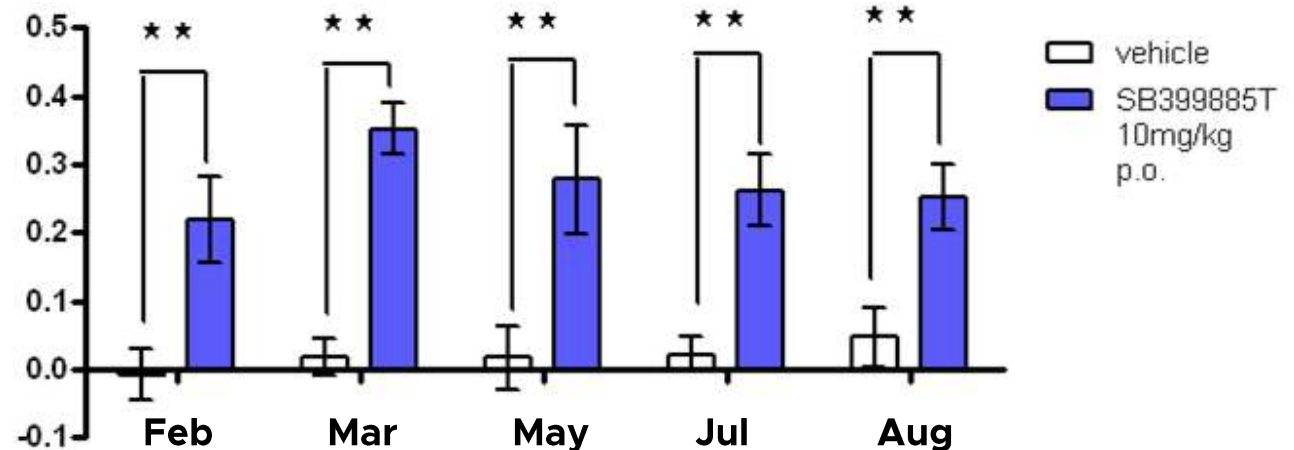
Protocol



Dose-response using a cognitive enhancer

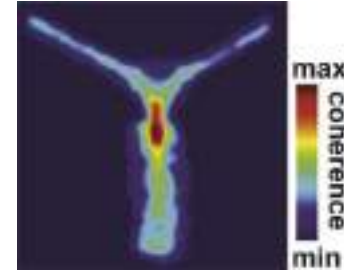


In-house reproducibility



Final thoughts for successful translation

- ✱ **Do good science (of course!)**
- ✱ **Know your model/assay/clinical endpoints**
 - If you don't, collaborate, or outsource!
- ✱ **Consider the throughput**
- ✱ **Automate tasks where possible**
 - Reduced stress
 - Higher throughput
 - Reduced experimenter bias
- ✱ **Include non-behavioural endpoints**
 - E.g. wireless LFP recording on the Y-maze
 - confirm HIPP-PFC engagement in your task / treatment
- ✱ **Encourage use of objective measures in clinical trials**
 - Capitalise on knowledge from preclinical research
 - Non-verbal tests provide greater reverse translation
 - E.g. virtual reality to assess spatial cognition



Final thoughts for successful translation

- * **Do good science (of course!)**
- * **Know your model/assay/clinical endpoints**
- * **Consider the throughput**

- * **Automate tasks where possible**

- Reduced stress
- Higher throughput
- Reduced experimenter bias

- * **Include non-behavioural endpoints**

- E.g. wireless LFP recording on the Y-maze to confirm HIPP-PFC engagement

- * **Use of objective measures in clinical trials**

- Non-verbal tests = greater reverse translation
- E.g. virtual reality game developed by researchers at UCL to test spatial memory

Thank You!





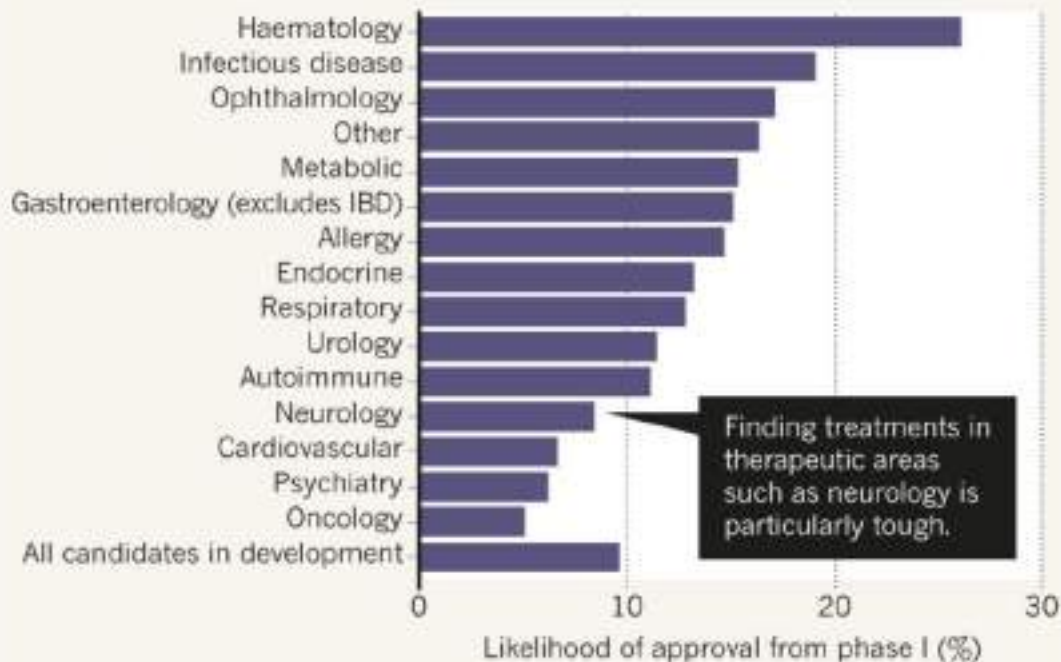
Extra slides

Clinical failure is high in CNS disorders

...though oncology and heart disease are similarly challenging....

HIGH FAILURE RATE

In 7,455 drug-development programmes from 2006 to 2015, fewer than 10% of experimental drugs were found to be safe and effective, and then approved for market.



Finding treatments in therapeutic areas such as neurology is particularly tough.

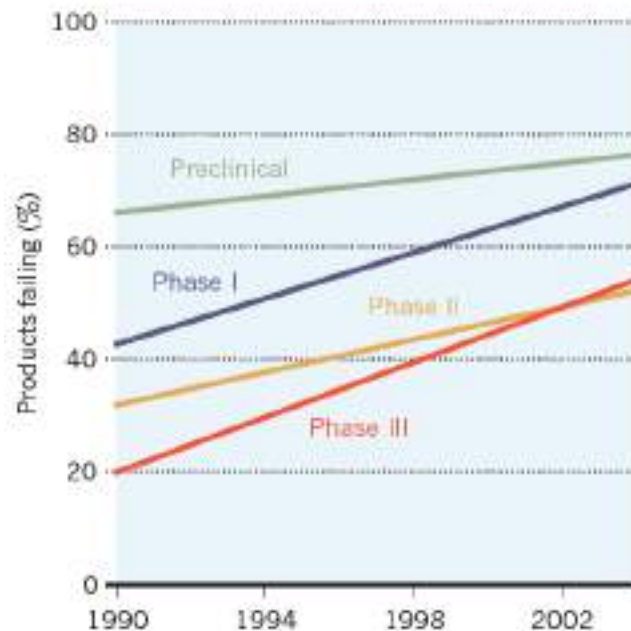
IBD, inflammatory bowel disease.

©nature

THE CLINICAL-TRIAL CLIFF

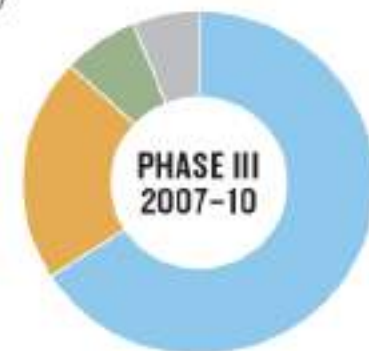
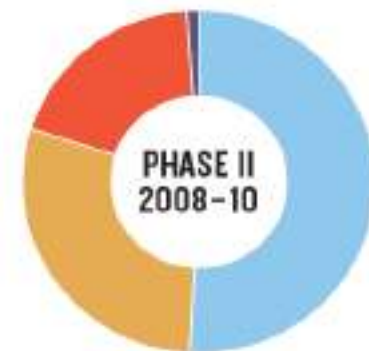
Drug companies are removing more compounds from the pipeline at all levels of testing than ever before.

For projects started between 1990 and 2004, the United States, Europe and Japan have seen sharp rises in the attrition of drugs tested in trials.



Most of the product failures in phase II and III trials are because researchers are unable to demonstrate efficacy or sufficient safety.

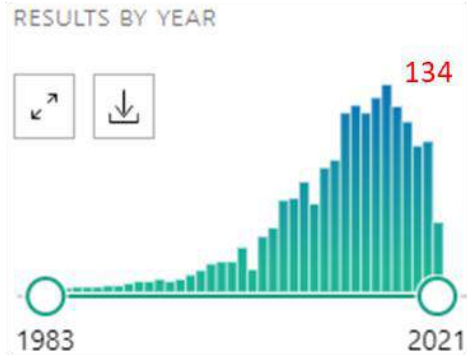
- Efficacy
- Safety
- Strategic
- Pharmacokinetics/ bioavailability
- Commercial/ financial
- Not disclosed



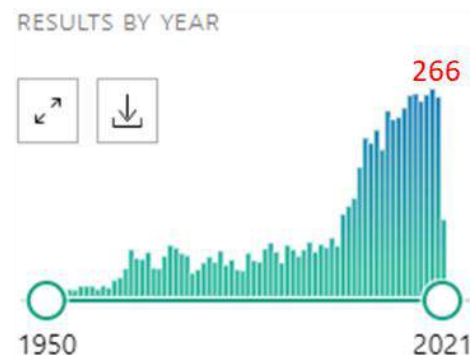
Source: <https://www.nature.com/news/2011/110928/full/477526a.html>

Publications bear out the enduring popularity of cognitive tests

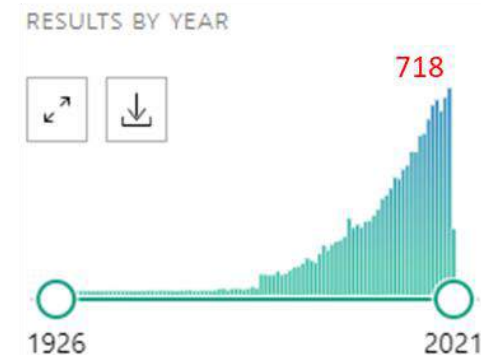
- Set shifting



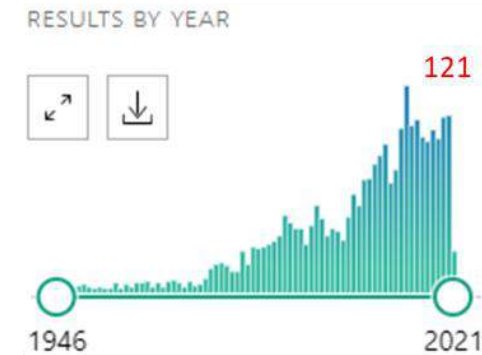
- Reversal learning



- ★ Spon. alternation



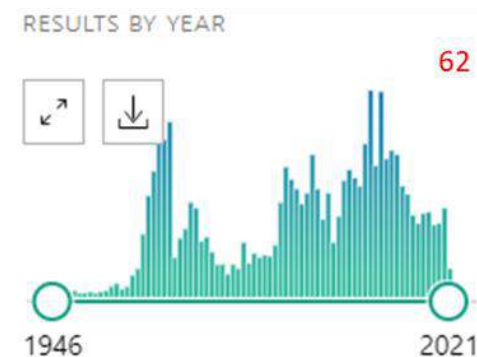
- T-maze



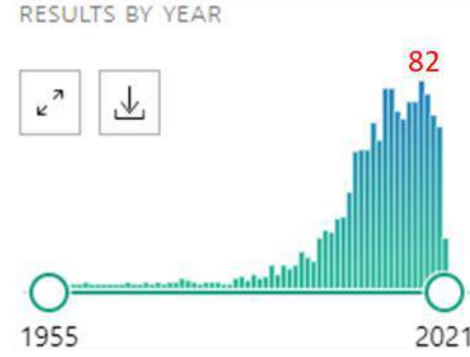
- ★ Water-maze



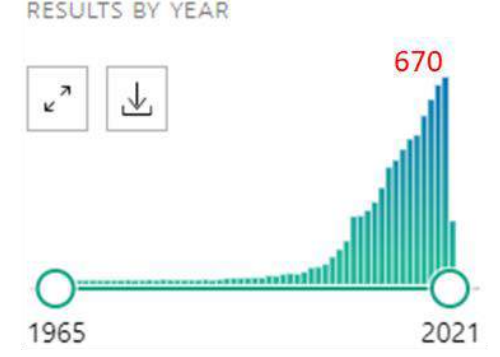
- Paired-assoc. learning



- Serial react. time



- ★ Novel obj. recog.



Use a test-battery if you can



Pharmacology & Therapeutics

Volume 122, Issue 2, May 2009, Pages 150-202



Associate editor: D. Süley

Using the MATRICS to guide development of a preclinical cognitive test battery for research in schizophrenia

Jared W. Young, Susan B. Powell, Victoria Rishbrough, Hugh M. Marston¹, Mark A. Geyer^{1,2}

PLOS ONE

OPEN ACCESS



PEER-REVIEWED

RESEARCH ARTICLE

A Comprehensive Behavioral Test Battery to Assess Learning and Memory in 129S6/Tg2576 Mice

Andrea Wolf, Björn Bauer, Erin L. Aigner, Tal Ashkenazy-Frimer, Anika M. S. Hartz

Published: January 25, 2010 • <https://doi.org/10.1371/journal.pone.0147731>

Neurobiology of Aging 34 (2003) 1891-1901



Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging



Review

A preclinical cognitive test battery to parallel the National Institute of Health Toolbox in humans: bridging the translational gap

Shikha Snigdha^{a,*}, Norton W. Milgram^b, Sherry L. Willis^c, Marylin Albert^d, S. Weintraub^e, Norbert J. Fortin^{e,g}, Carl W. Cotman^{a,b}

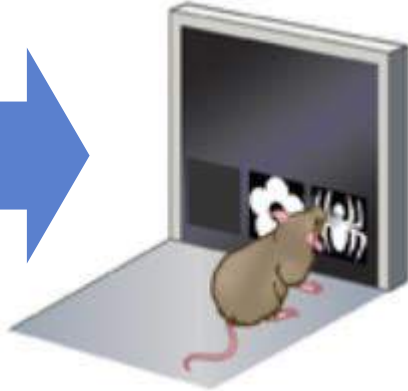
Touchscreen automation

Clinical (CANTAB)



Matching to Sample

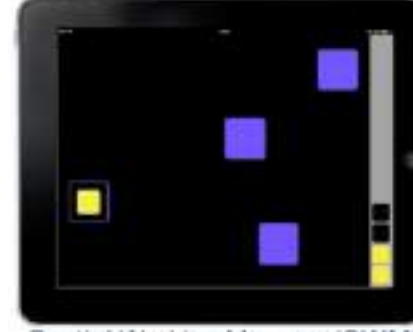
preclinical



<https://www.cambridgecognition.com/>

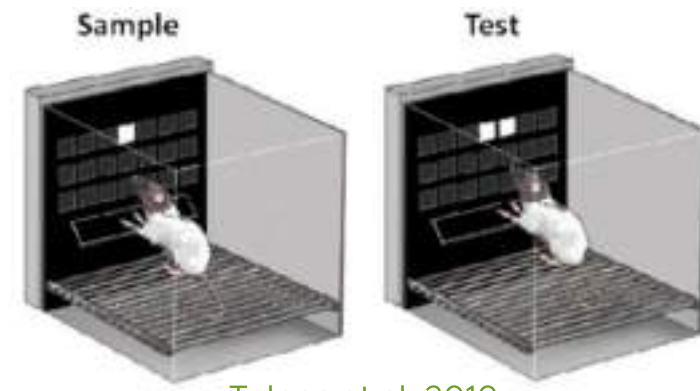
[Nithianantharajah et al., 2015](#)

Clinical (CANTAB)



Spatial Working Memory (SWM)

preclinical



[Talpos et al, 2010](#)