

**4<sup>ο</sup> Πανελλήνιο Συνέδριο ΕΛ.Ε.Φ.Ι. 20-22 Ιουνίου 2019, Αθήνα**

**Φαρμακευτική Ιατρική και Κλινική Έρευνα στον 21<sup>ο</sup> Αιώνα:  
Προσαρμογή στην Ψηφιακή Υγεία και Ενδυνάμωση του Ασθενή**

**Προκλινική και Μεταφραστική Έρευνα στην Ψυχοφαρμακολογία**

**Κατερίνα Αντωνίου**  
**Αναπληρώτρια Καθηγήτρια Φαρμακολογίας**  
**Ιατρικό Τμήμα**  
**Πανεπιστήμιο Ιωαννίνων**  
**[kantoniu@cc.uoi.gr](mailto:kantoniu@cc.uoi.gr)**

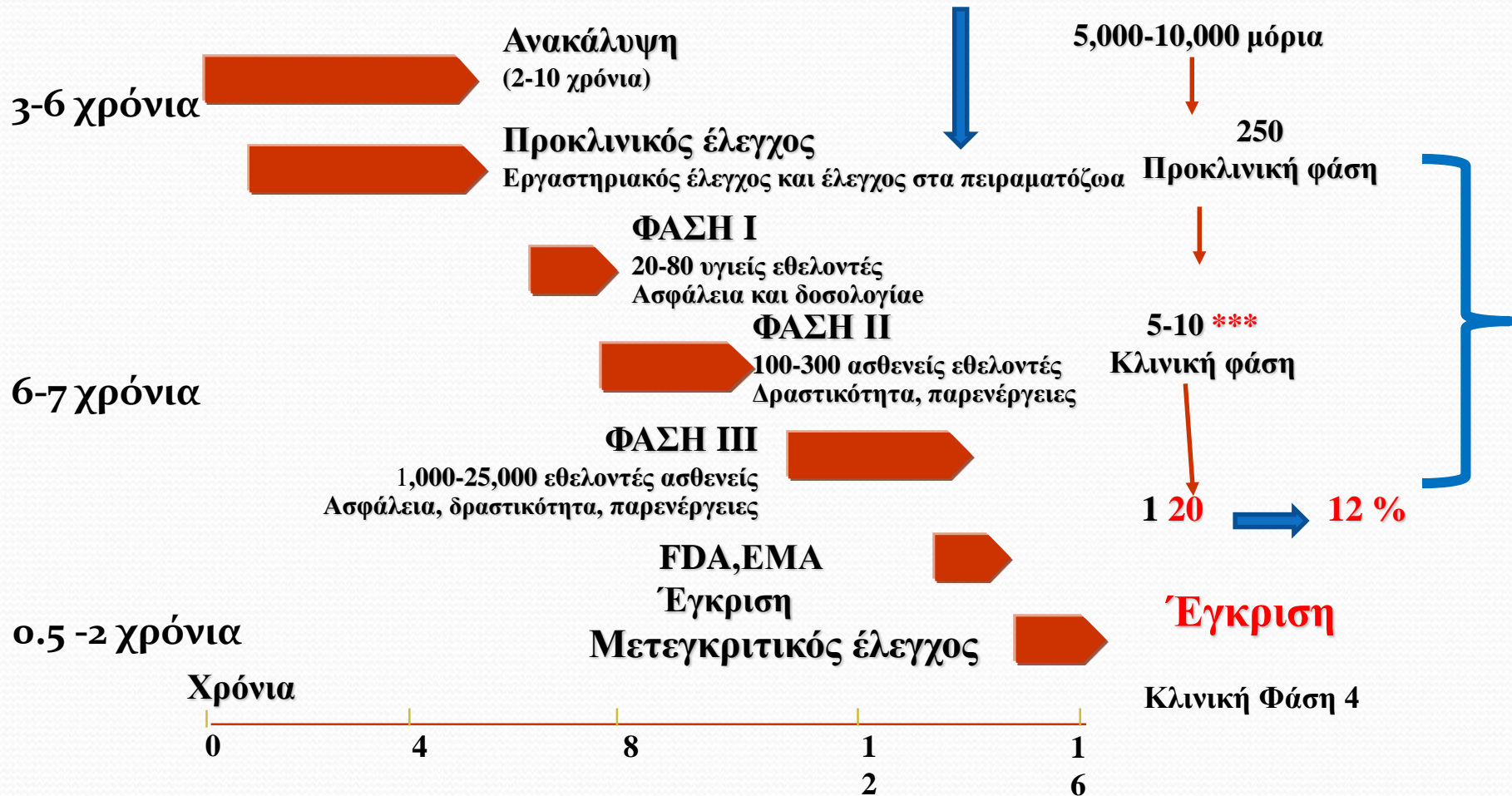
**Εισαγωγή**

**Ψυχοφαρμακολογία και  
Μεταφραστική Έρευνα – Ερωτήματα  
προς συζήτηση**

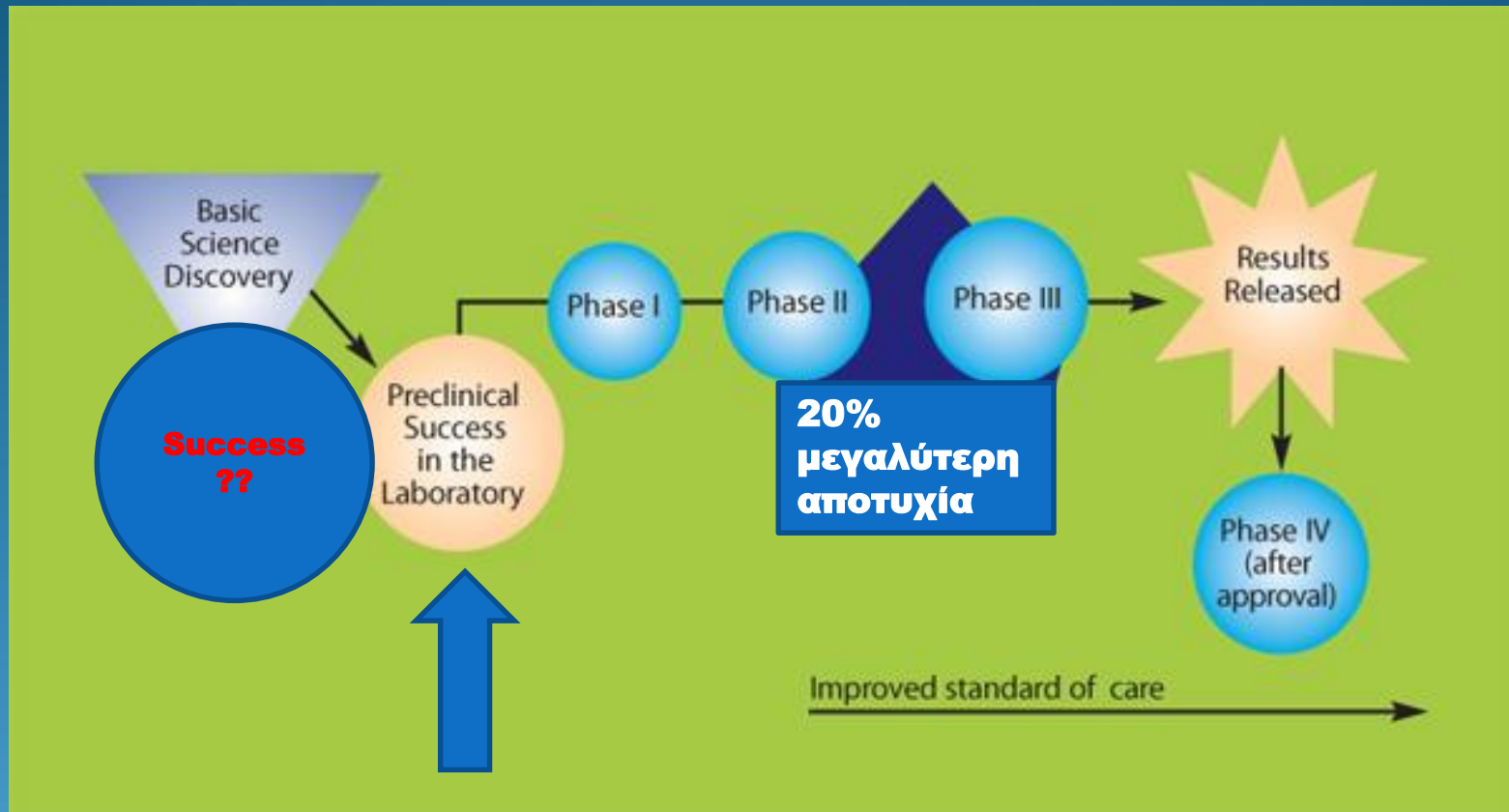
**Παρουσίαση αποτελεσμάτων  
Προοπτικές -Συμπεράσματα**

# **Εισαγωγή**

# Η πορεία ανακάλυψης και ανάπτυξης του φαρμάκου



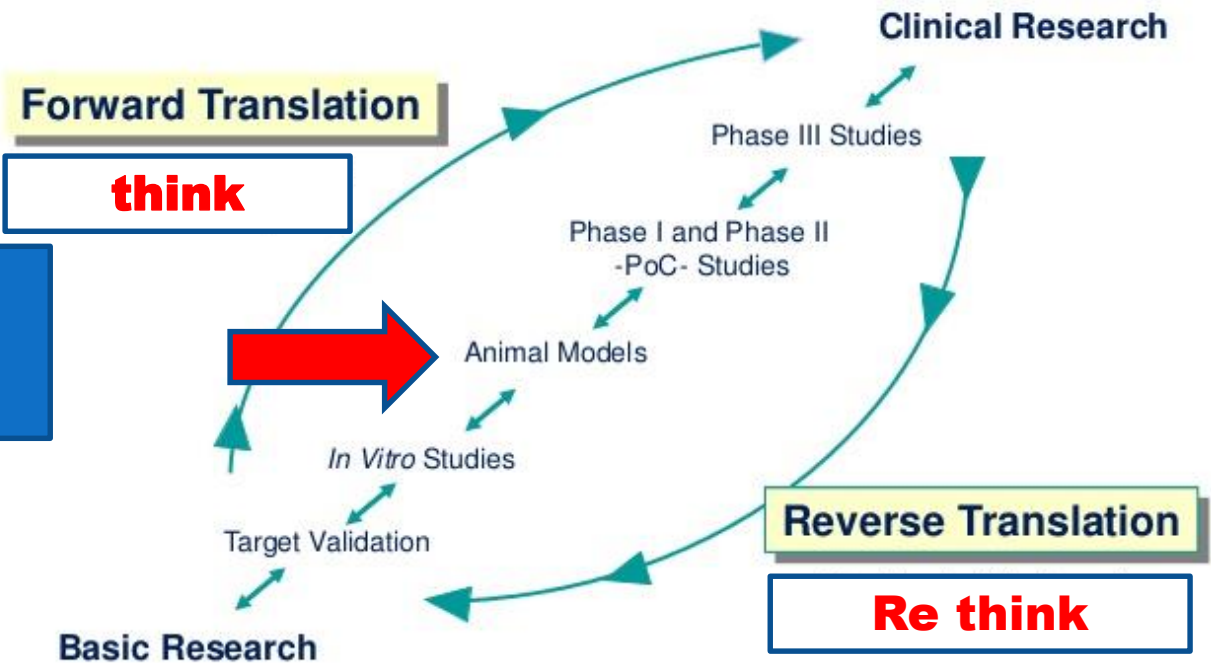
# Η πορεία ανάπτυξης του φαρμάκου



**Key issues : re-think and further discuss for CNS Disorders**

## Translational medicine in pharma

**Μοντελοποίηση**



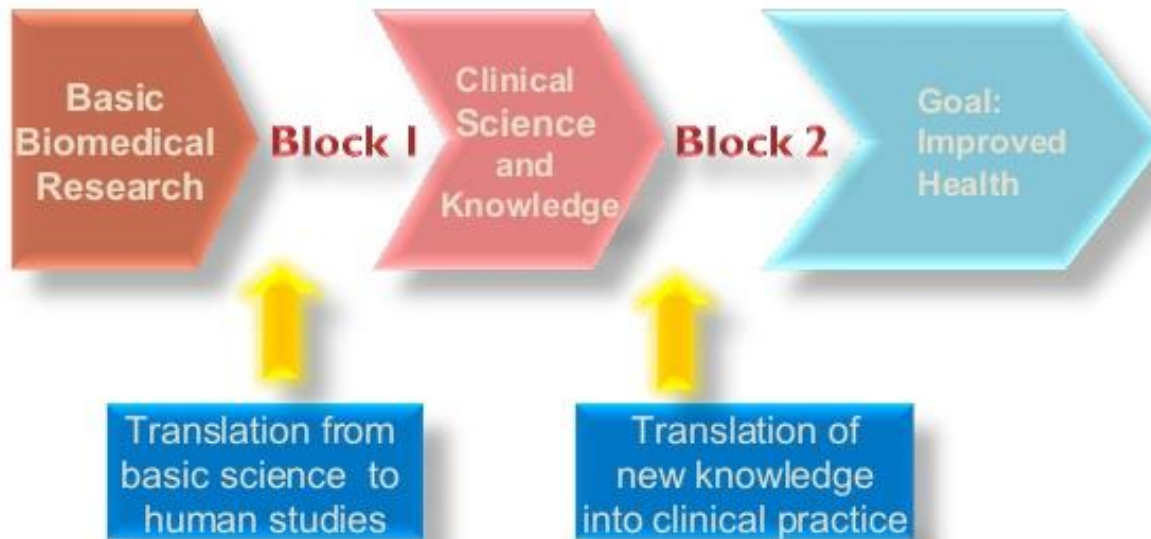
[van Gool et al, Drug Disc. Today 2010]

## Drug Development

- Drug design-Computational
- Radioligand binding studies
- Signaling experiments
- Preclinical in vivo studies



# THE TWO TRANSLATIONAL BLOCKS



**DATA- INFORMATION-KNOWLEDGE**

**Ψυχοφαρμακολογία και  
Μεταφραστική Έρευνα – Ερωτήματα  
προς συζήτηση - Προοπτικές**



# Πειραματικά μοντέλα – Πρότυπα Μοντελοποίηση

- Αναπαραγωγή διαταραχής ΚΝΣ σε πειραματόζωα ?
- **Ιδανικό μοντέλο ?** (ταύτιση στην αιτιολογία, στα συμπτώματα, στην απάντηση σε θεραπευτική αντιμετώπιση? Προσομοίωση?)



- **Χρήσιμο** είναι εάν: **face validity**  
**construct validity**  
**predictive validity**  
**reliability**

# Πειραματικά μοντέλα – Πρότυπα - Μοντελοποίηση

**Κατάθλιψη**

**Εξαναγκασμένη κολύμβηση ?**

**Χρόνιο ήπιο στρες ?**



**Ανηδονία**



**Ελεγχος αντικαταθλιπτικής Δράσης**

**Θηλυκά – Αρσενικά ?**

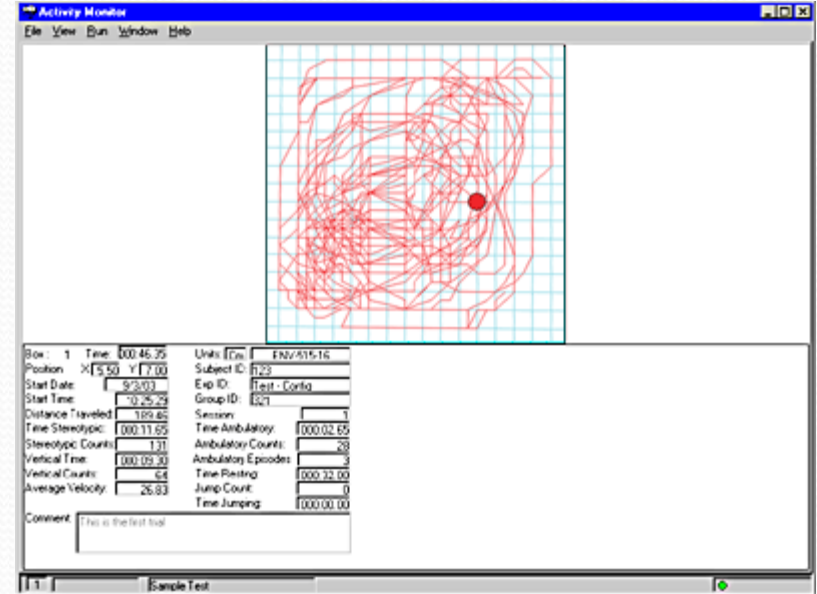
**Κολύμβηση – επίπλευση - αναρίχηση**



# Πειραματικά μοντέλα – Πρότυπα - Μοντελοποίηση

## Ψύχωση

## Δράση αμφεραμίνης ?

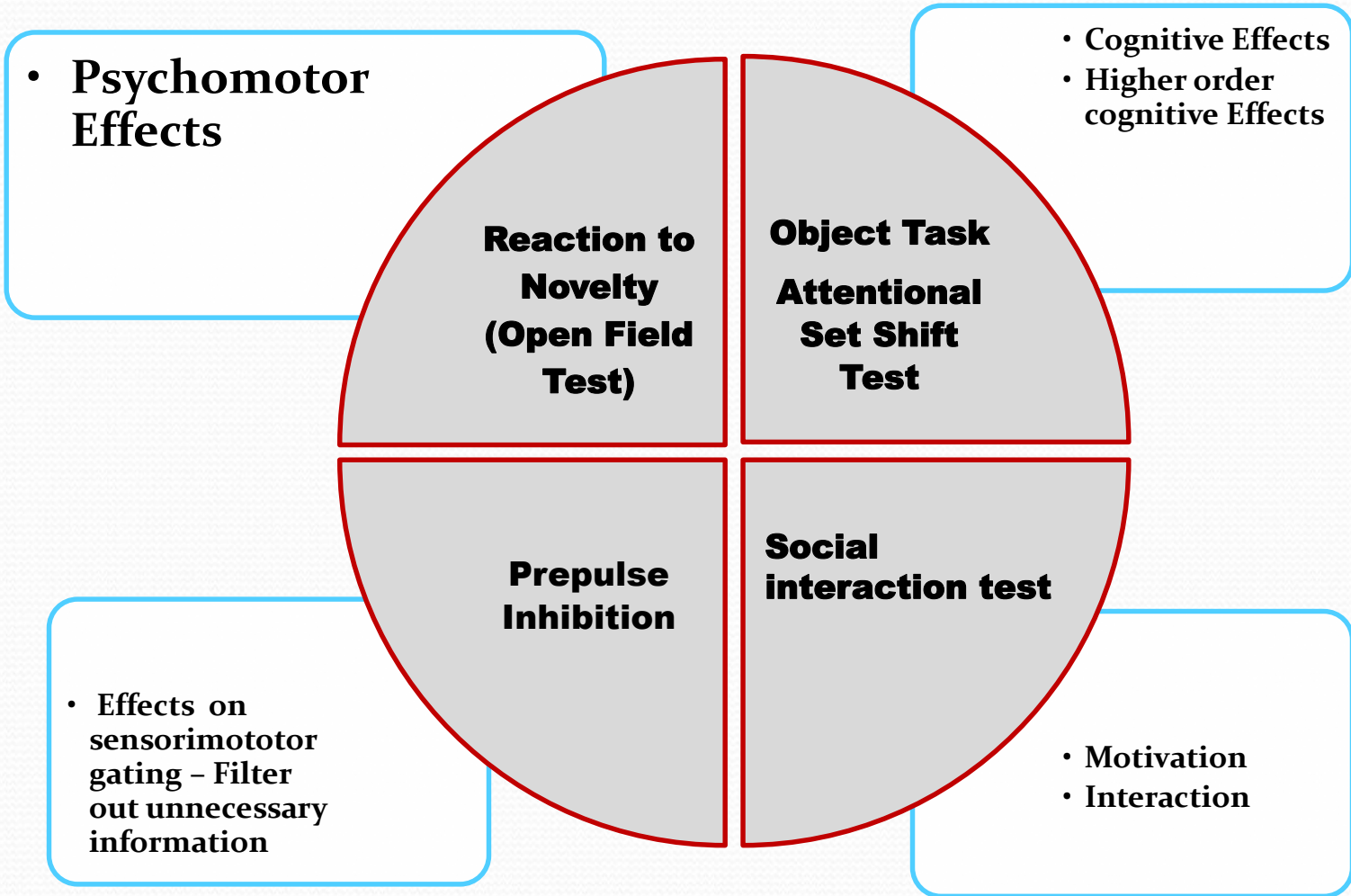


**Πιθανή αντιψυχωσική Δράση**



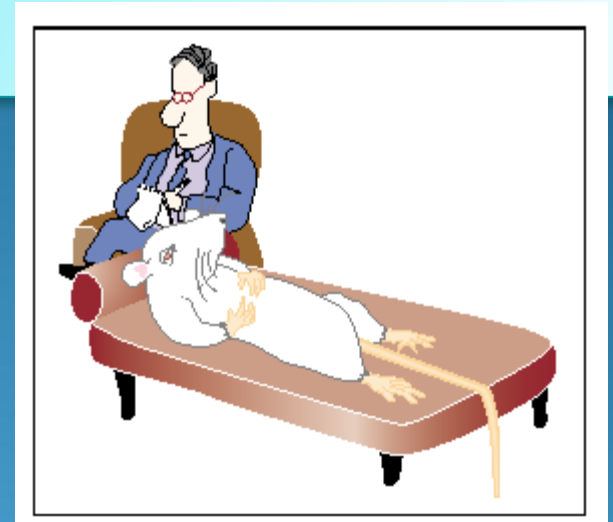
# Πειραματικά μοντέλα – Πρότυπα - Μοντελοποίηση

## Ψυχωση



- **Ιδανικό μοντέλο προσομοίωσης Διαταραχής ΚΝΣ?**
- **Προσέγγιση συμπτωματολογίας ?**
- **Συσχέτιση με Νευροβιολογικό Υπόστρωμα**
- **Φαινότυπος - Ενδοφαινότυπος – Μικροφαινότυπος**

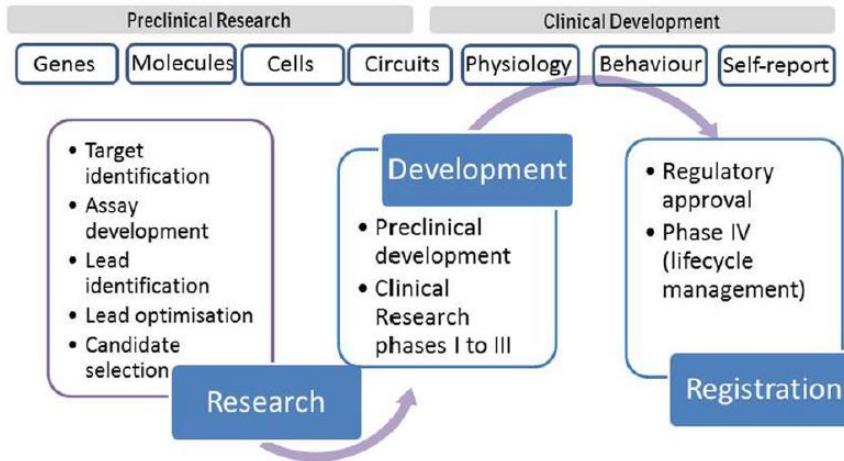
➤ **Απαρτίωση προσεγγίσεων**



- **Μελέτες συμπεριφοράς – Δείκτες – Εστίαση**
- **Συσχέτιση με νευροβιολογικούς δείκτες**
- **Φαινότυπος - Ενδοφαινότυπος- Μικροφαινότυπος**
- **Απαρτίωση προσεγγίσεων**

# Ερωτήματα προς συζήτηση - Προοπτικές

A major challenge in drug discovery in psychiatry is the **translation from pre-clinical to clinical settings**



RDoC combined with advances in the neuroscience „tool box“ should increase alignment between preclinical research & clinical development



Transferability of preclinical evaluations in animal models to clinical measures in humans is challenging in neuropsychiatric research



Focus on discrete traits as components of more complex phenomena

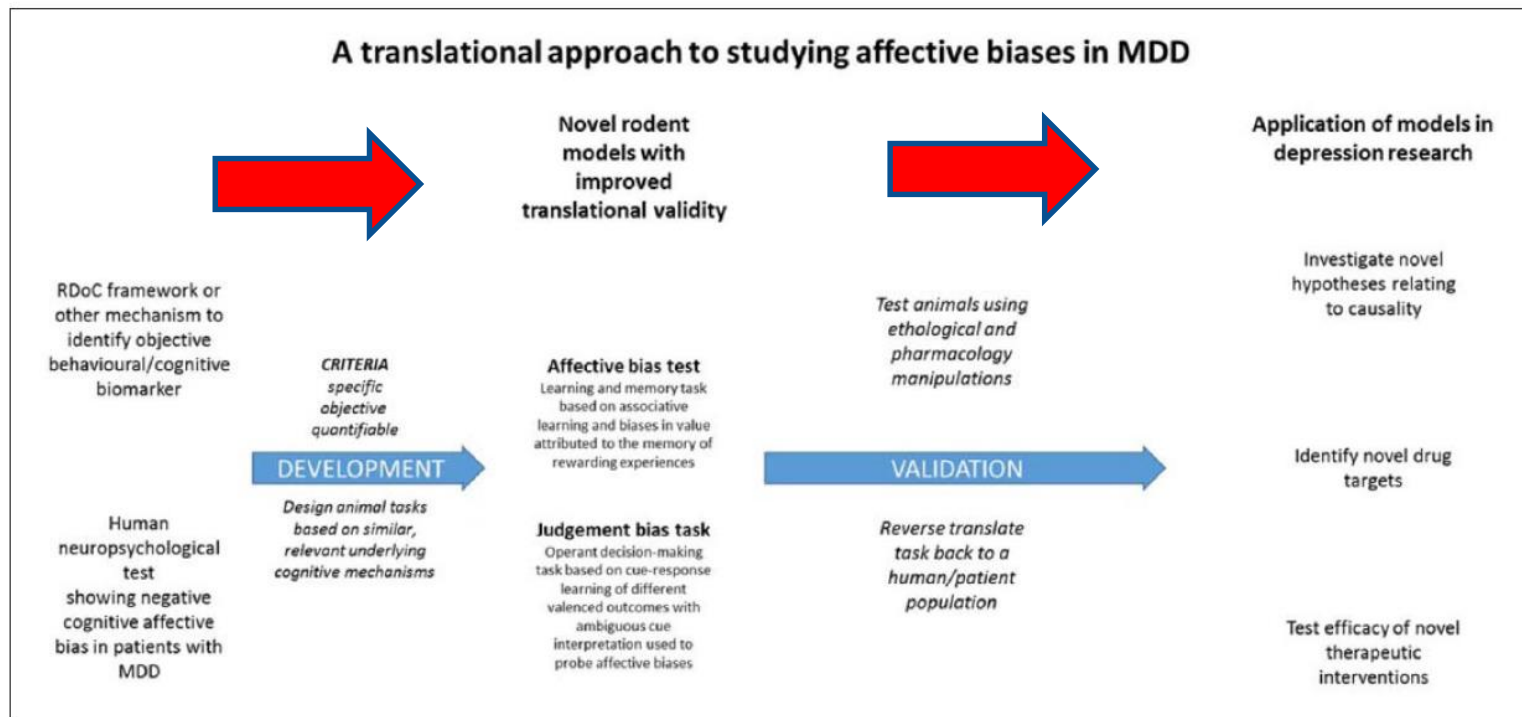
**Figure 2.** The complexity of the human brain and behaviour poses a challenge to neuropsychiatric drug development. Focus on discrete traits as components of more complex phenomena.

\* **Research domain criteria (RDoC)**

**Nicholson and Somer, 2018  
Brain and Neuroscience Advances**



# Ερωτήματα προς συζήτηση - Προοπτικές



**Figure 2.** Overview of an approach to develop better translational behavioural methods to study relevant neuropsychological characteristics of psychiatric disorders and improve integration of fundamental biology, preclinical drug discovery and development, and clinical studies. See also discussion in Robinson, 2018 in relation to major depressive disorder.

**Robinson, 2018,  
Brain and Neuroscience Advances**

**Sex differences in hypothalamic-pituitary-adrenal axis: An **obstacle** to antidepressant drug development**

**Kokras N., Hodes G., Bangasser D. and Dalla C.  
Br J Pharmacol, 2019**



**Sex differences contribute **to the failure** of novel HPA axis-based drugs in clinical trials**

**Animal and human psychopharmacology  
with clinical utility in the treatment of psychiatric disorders.**

**The main theme is to develop a new paradigm for drug discovery  
that **questions the claim that animal models or  
assays fail adequately to predict Phase 3 clinical trials.****

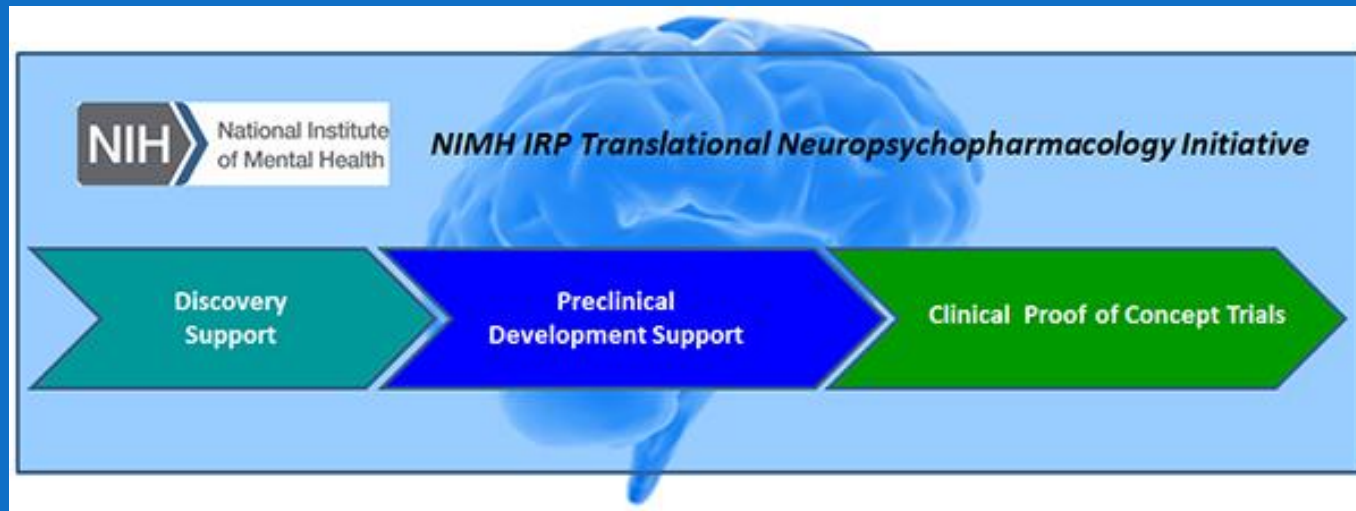
**A new paradigm is advocated that stresses the importance of  
intermediate staging points between these extremes **that  
depend on suitable translation of findings from animal studies  
to Phase 1 or Phase 2.****

**Translational Neuropsychopharmacology  
Editors: Robbins, Trevor W., Sahakian, Barbara J. (Eds., 2016)**

**The National Institute of Mental Health (NIMH) has become increasingly aware of the reduced investment by pharmaceutical companies in the development of therapeutics for treating psychiatric disorders despite the unmet medical need.**

**Consequently, the NIMH Intramural Research Program (IRP) is proposing to re-invigorate psychiatric drug discovery by facilitating and de-risking the discovery and development of novel treatments.**

**Translational Neuropsychopharmacology Task Force (TNTF).**



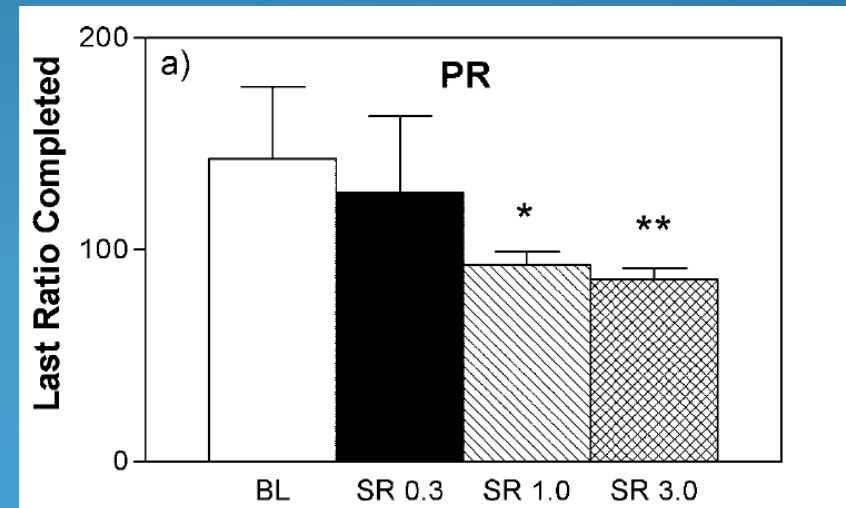
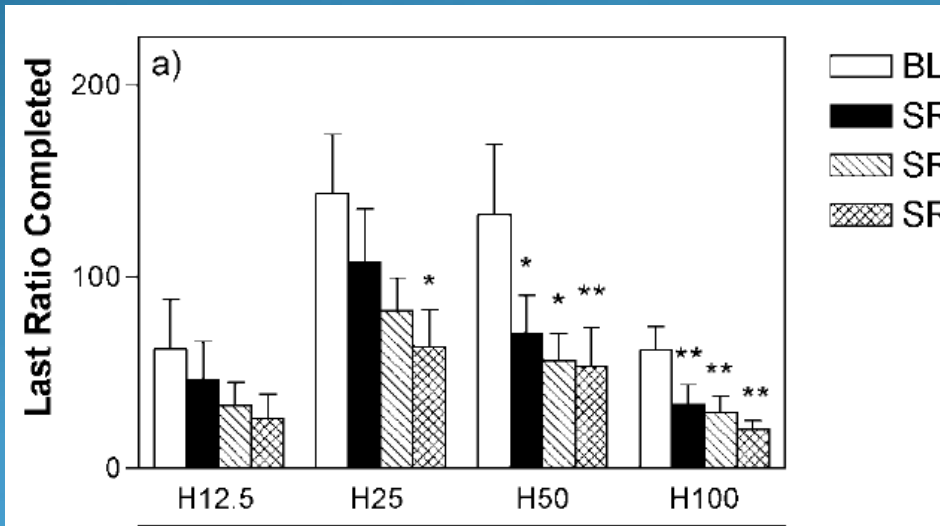
**Παρουσίαση αποτελεσμάτων  
Συμπεράσματα**

# **Παρουσίαση αποτελεσμάτων**

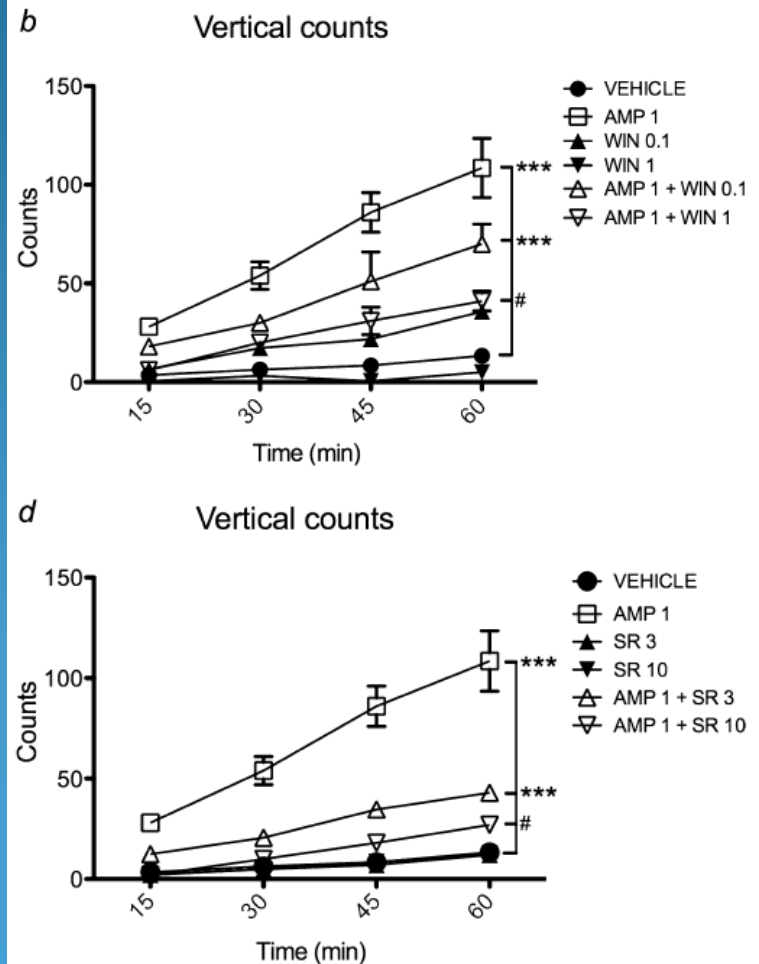
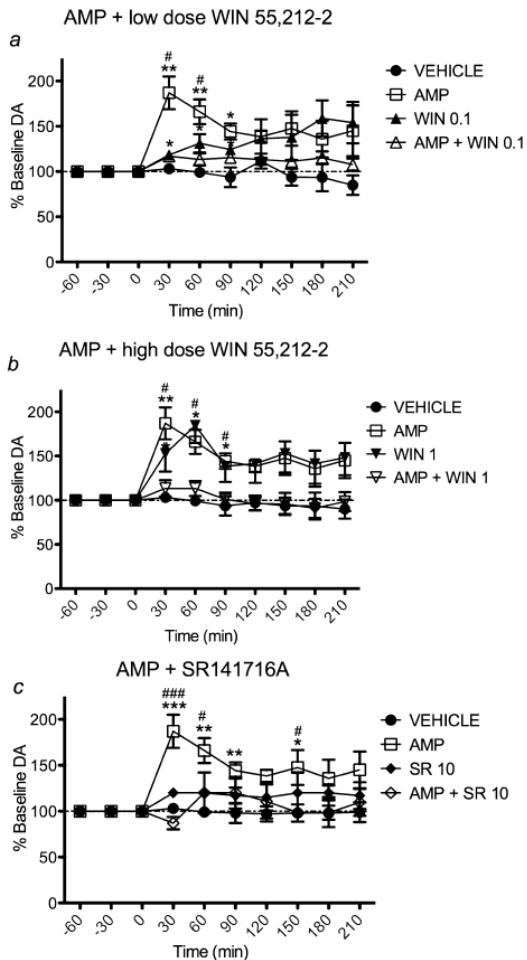
## **Συμπεράσματα**



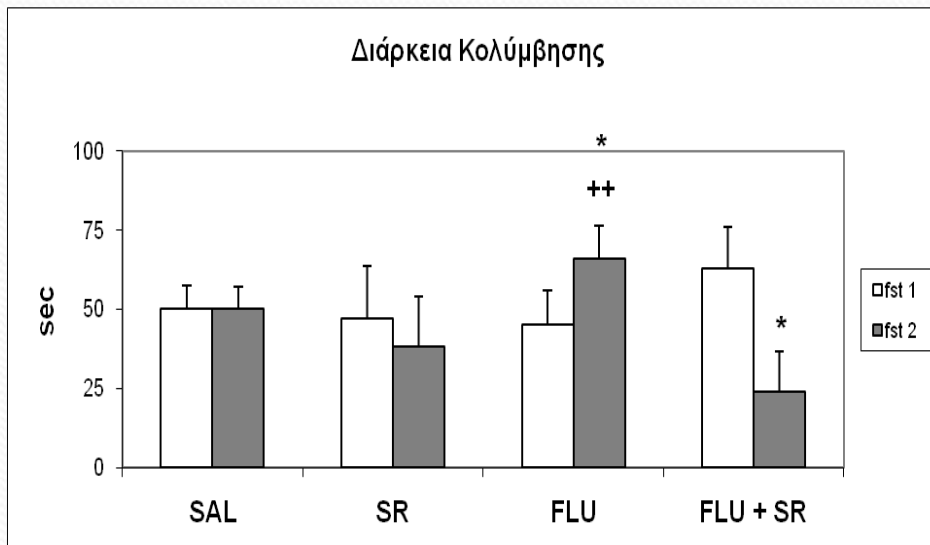
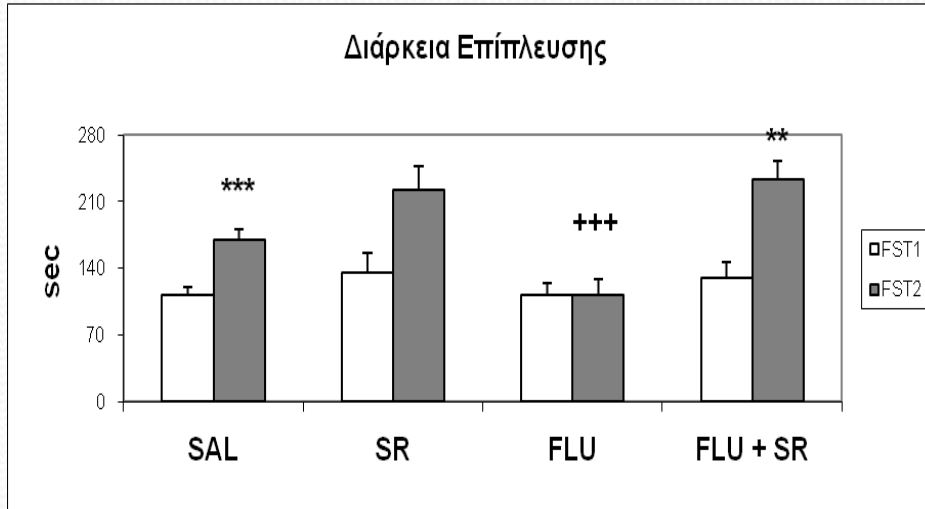
**J Pharmacol Exp Ther.** 2003 The cannabinoid CB1 antagonist N-piperidiny-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (SR-141716A) differentially alters the reinforcing effects of heroin under continuous reinforcement, fixed ratio, and progressive ratio schedules of drug self-administration in rats. **Solinas M<sup>1</sup>, Panlilio LV, Antoniou K, Pappas LA, Goldberg SR**



**Polissidis et al., Cannabinoids negatively modulate striatal glutamate and dopamine release and behavioural output of acute D-amphetamine. Behav Brain Res. 2014**



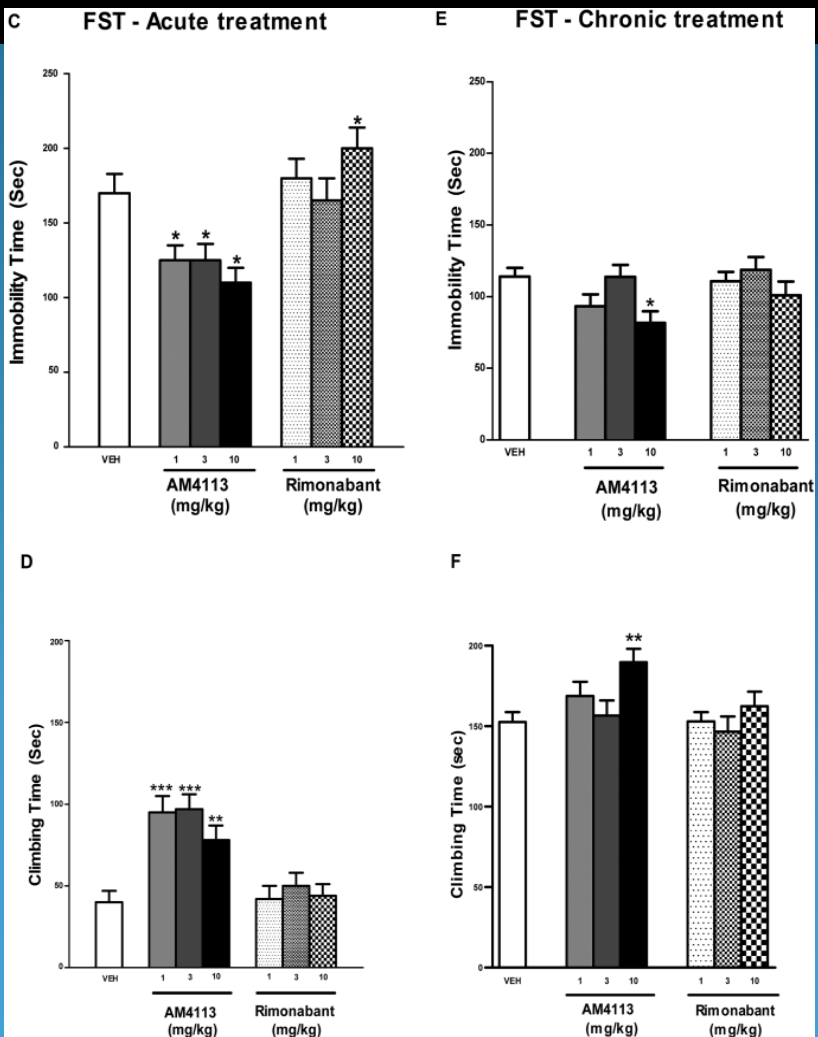
# ΑΛΛΑ?



\*\*\*  $p < 0.001$ ,  
\*\*  $p < 0.01$ ,  
\*  $p < 0.05$  για  
στατιστικά  
σημαντικές  
διαφορές μεταξύ  
πρώτης και  
δεύτερης  
δοκιμασίας  
εξαναγκασμένης  
κολύμβησης.

+++  $p < 0.001$ , ++  
 $p < 0.01$ ,  
+  $p < 0.05$  για  
στατιστικά  
σημαντικές  
διαφορές της  
φλουοξετίνης με  
τις υπόλοιπες  
ομάδες

**Int J Neuropsychopharmacol. 2016 The CB1 Neutral Antagonist AM4113 retains the Therapeutic Efficacy of the Inverse Agonist Rimonabant for Nicotine Dependence and Weight Loss with Better Psychiatric Tolerability.**  
**Gueye AB, Pryslawsky Y, Trigo JM, Poulia N<sup>1</sup>, Delis F, Antoniou K, Loureiro M, Laviolette SR, Vemuri K, Makriyannis A, Le Foll B.**



**Problems and crisis in  
Preclinical research ?**

**Reproducibility and predictability**

**Study design  
Analysis  
Interpretation**

# Crisis in preclinical research

## Different pattern/ Different baseline

- Preclinical Research in CNS – Academy
- Significant impact on the design of clinical research and clinical trials



**Crisis in  
preclinical  
science**

- **Symposium**
- **Workshops**

**Data  
sharing  
Information  
Knowledge**

**Difficult  
Project**

- **Challenge**
- **Need**

**Academia - Industry - Agency/Regulatory**

preclinical research

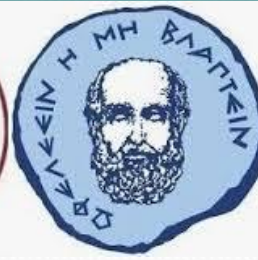


Sufficient productive transferability from animals  
to humans

Maximize the value

**Crisis in preclinical research**

- 1) Wrong direction in clinical research**
- 2) Block the DEVELOPMENT of new therapeutic strategies**



Αλεξία Πολυσίδη  
Ανδρέας Γαλανόπουλος  
Όλγα Χουλιάρα  
Φωτεινή Δελή  
Νίκος Κοκρας  
Ναυσικά Πούλια  
Χάρης Μπρακατσέλος  
Γιασεμή Κουτμάνη

Κική Θερμού  
Αχιλλέας Γραβάνης  
Γιαννης Χαραλαμπόπουλος  
Νίκος Πιτσίκας  
Γιώργος Παναγής  
Χριστίνα Δάλλα  
Πάνος Πολίτης



Ζ. Παπαδοπούλου - Νταϊφώτη  
Χ. Σπυράκη



Σας ευχαριστώ πολύ για την προσοχή σας!

**Basic Research**

**Preclinical Research**

e.g.

**Open Field  
paradigm**

**Forced swim test**

**Cognitive tasks**

**Clinical research**

**Clinical Trials**

**Training Phase**  
T1= 3 min



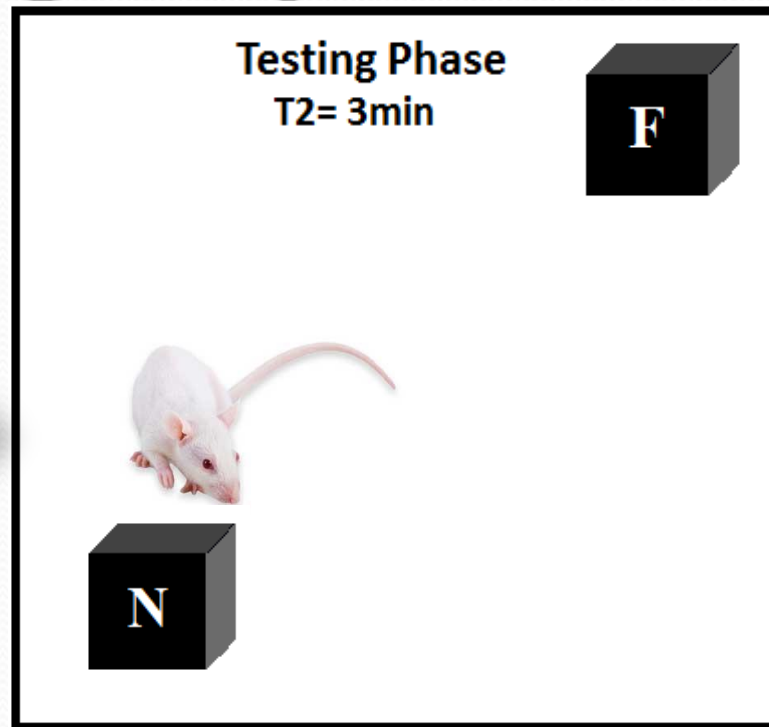
A diagram of the training phase. It features a white mouse in the center, enclosed in a white diamond-shaped frame. Two black 3D cubes are positioned at the top left and top right corners. The text "Training Phase" and "T1= 3 min" is located at the top.

Μετά από 1h

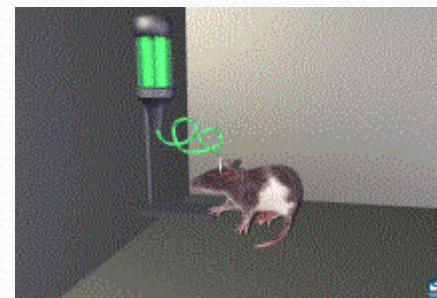


A red arrow pointing from the training phase to the testing phase, with the text "Μετά από 1h" (After 1h) written inside it.

**Testing Phase**  
T2= 3min

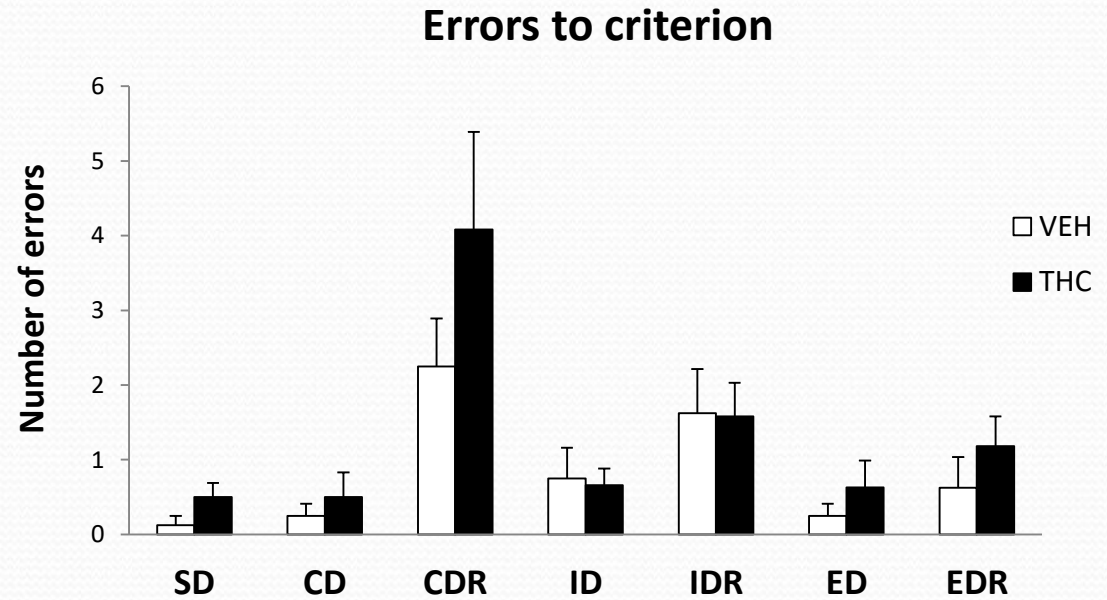
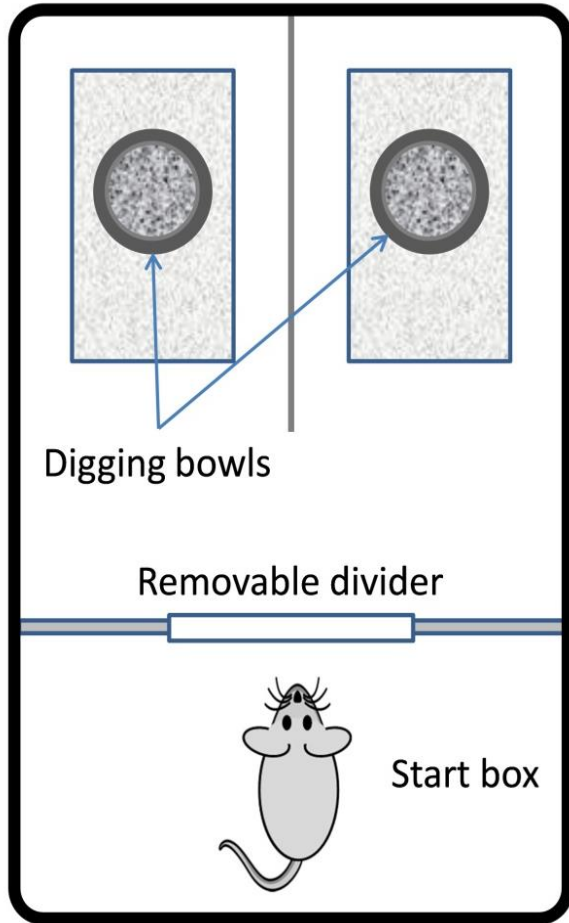


A diagram of the testing phase. It features a white mouse in the center. A black 3D cube with the letter "N" is at the bottom left, and another black 3D cube with the letter "F" is at the top right. The text "Testing Phase" and "T2= 3min" is located at the top.





# Μη επίδραση στις ανώτερες εκτελεστικές λειτουργίες





## History of the development of the major classes of drug used in psychiatric disorders\*

Timeline	Anxiolytics	Antidepressants	ADHD	Antipsychotics	Mood stabilisers
Pre-1900	alcohol, opiates	-	-	-	-
Early 20 <sup>th</sup> century	paraldehyde, chloral hydrate, and bromides barbiturates	barbiturates	-	barbiturates	-
Mid 20 <sup>th</sup> century	benzodiazepines tricyclic antidepressants	monoamine oxidase inhibitors tricyclic antidepressants	benzedrine (racemic amphetamine) methylphenidate	chlorpromazine haloperidol clozapine	lithium
Late 20 <sup>th</sup> century	alpha-1 subunit selective benzodiazepine SSRIs SNRIs receptor blocking antidepressants	SSRIs NaRI SNRIs receptor blocking antidepressants	mixed amphetamine salts, modified amphetamine/methylphenidate formulations	serotonin and dopamine antagonists dopamine partial agonists	antiepileptics serotonin and dopamine antagonists
Early 21 <sup>st</sup> century	gabapentinoids	ketamine	atomoxetine guanfacine, clonidine	-	-

serendipity

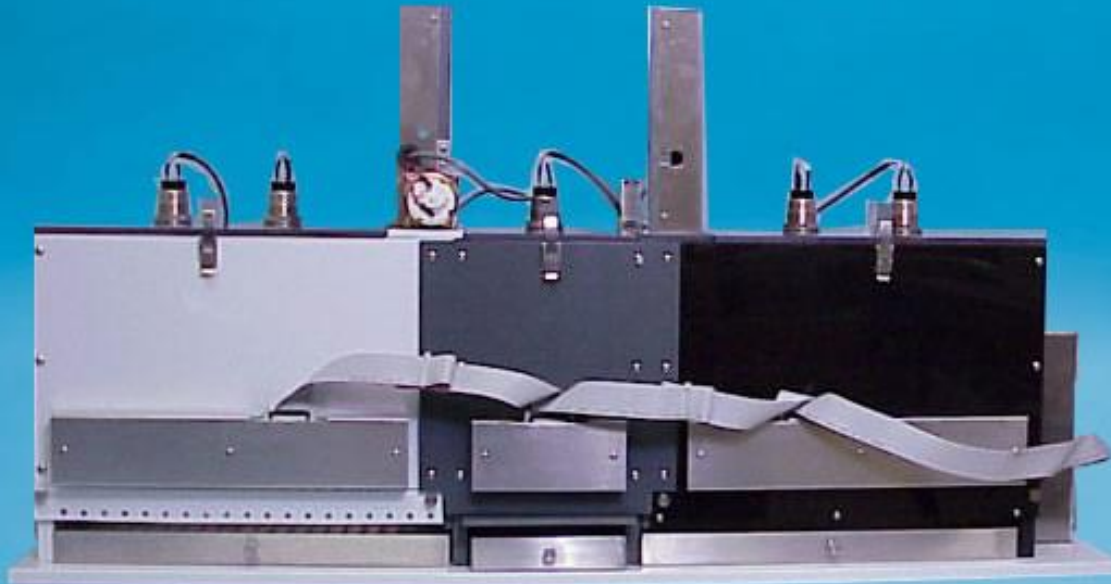
rational design

\* This is not designed to provide an exclusive list of all drugs developed in these areas but rather to illustrate the timeline and introduction of the major classes and their clinical uses

**Figure 1.** Drugs have been used to modify behaviour throughout humanity; however, the clinical use of drugs for specific conditions really developed from the start of the 20th century. This overview illustrates the timeline associated with the major classes of drugs used to treat psychiatric disorders. Although defined by their therapeutic target, the figure also indicates (arrows) where the same drugs have multiple therapeutic indications. An alternative approach to classification of psychiatric drugs is based on their psychopharmacology. Referred to as 'Neuroscience-Based Nomenclature' (<http://www.nbn2.com/>), this initiative has recategorised these drug treatments based on their pharmacology and mode of action rather than their first therapeutic indication.



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**The National Institute of Mental Health (NIMH) has become increasingly aware of the reduced investment by pharmaceutical companies in the development of therapeutics for treating psychiatric disorders despite the unmet medical need. Consequently, the NIMH Intramural Research Program (IRP) is proposing to re-invigorate psychiatric drug discovery by facilitating and de-risking the discovery and development of novel treatments. Support for the discovery and development of new treatments for psychiatric disorders including target validation, biomarker development, IND enabling studies, and Phase I safety / tolerability and Phase II proof of concept studies are all in scope for this important NIMH IRP initiative.**

**To steer this initiative the NIMH IRP has**