4ο Πανελλήνιο Συνέδριο ΕΛ.Ε.Φ.Ι. 20-22 Ιουνίου 2019, Αθήνα

Φαρμακευτική Ιατρική και Κλινική Ερευνα στον 21ο Αιώνα: Προσαρμογή στην Ψηφιακή Υγεία καιΕνδυνάμωση του Ασθενή

Προκλινική και Μεταφραστική Ερευνα στην Ψυχοφαρμακολογία

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Εισαγωγή

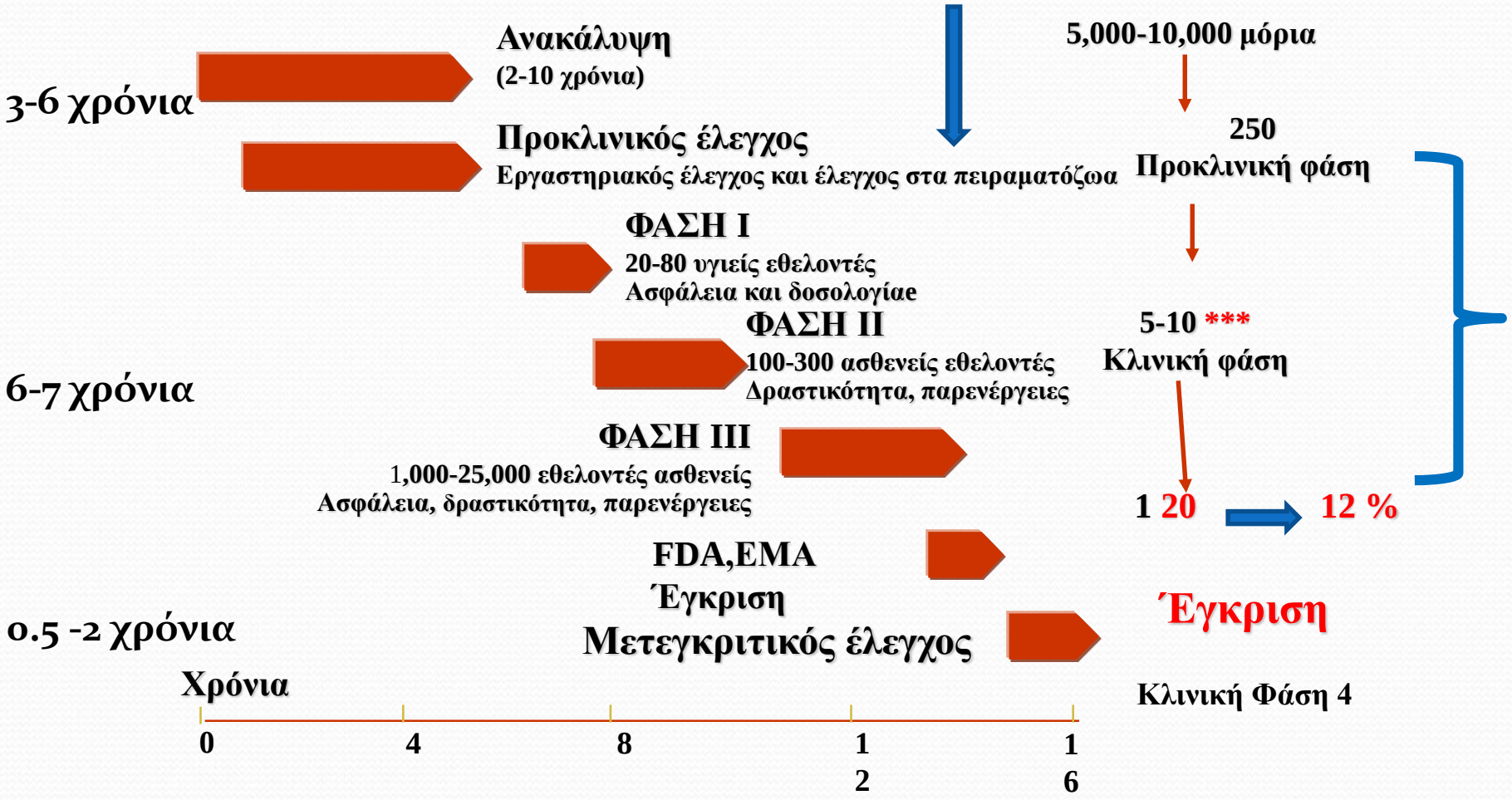
Ψυχοφαρμακολογία και Μεταφραστική Έρευνα – Ερωτήματα προς συζήτηση

Παρουσίαση αποτελεσμάτων

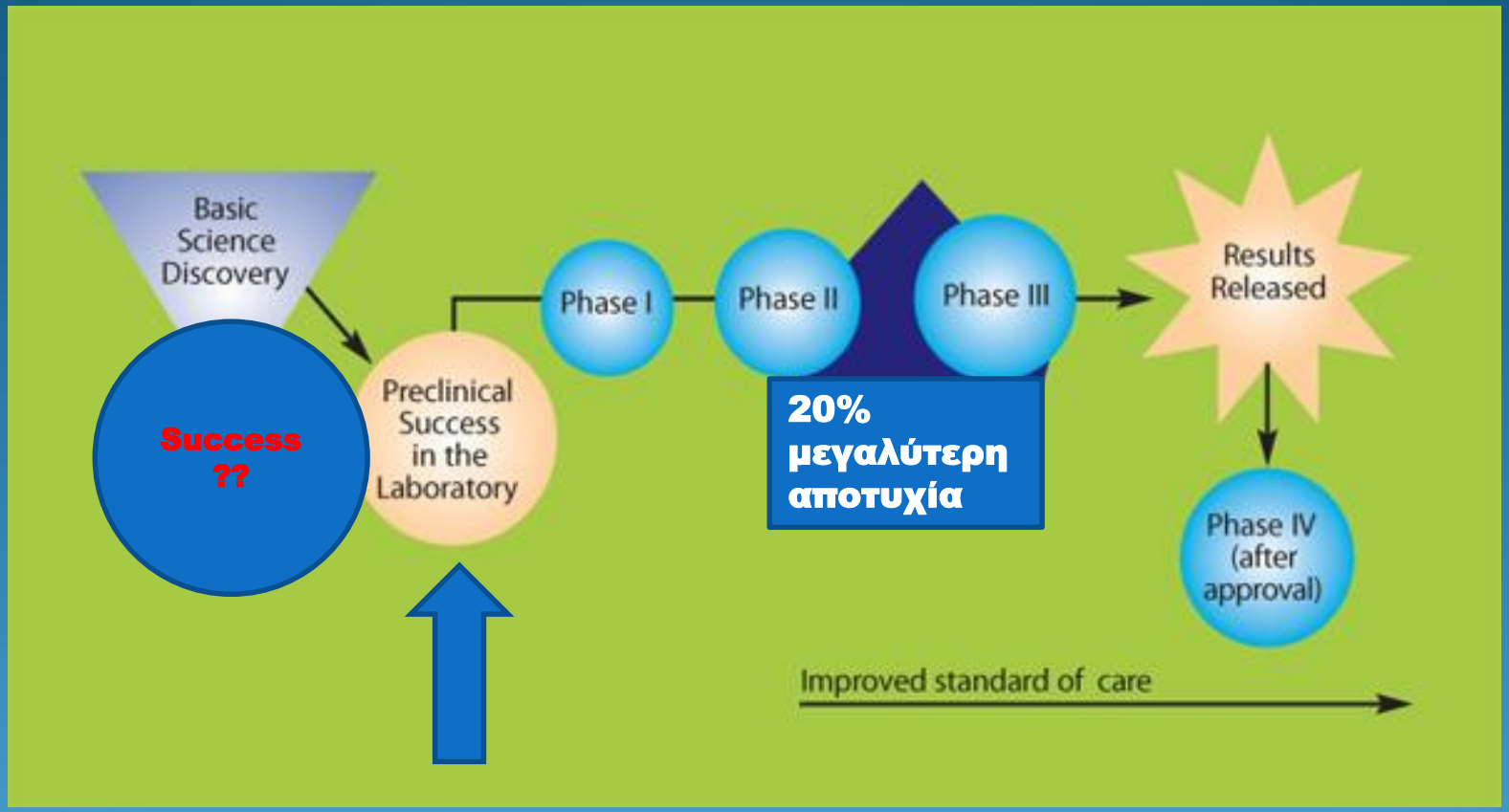
Προοπτικές -Συμπεράσματα

Εισαγωγή

Η πορεία ανακάλυψης και ανάπτυξης του φαρμάκου



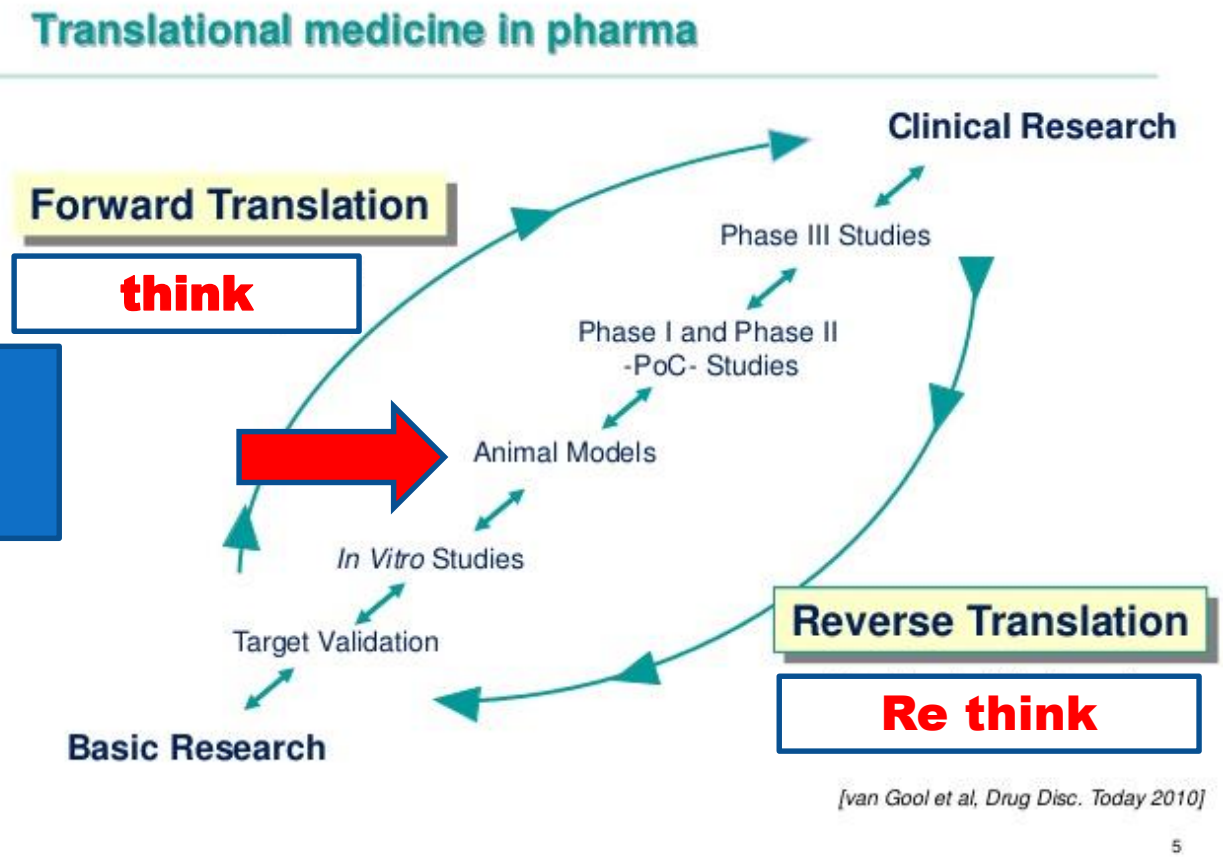
Η πορεία ανάπτυξης του φαρμάκου



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

Information on Drug Development

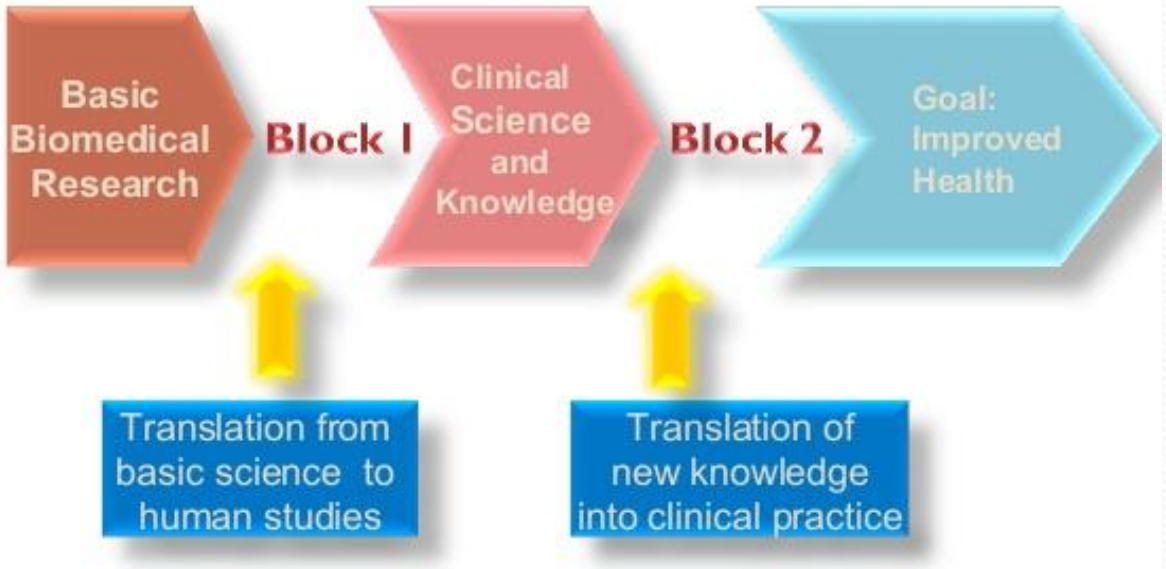
Μοντελοποίηση



Drug Development

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

THE TWO TRANSLATIONAL BLOCKS

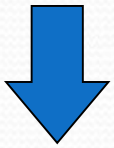


DATA- INFORMATION-KNOWLEDGE

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 ?

Θηλυκά – Αρσενικά ?

Κολύμβηση – επίπλευση - αναρίχηση

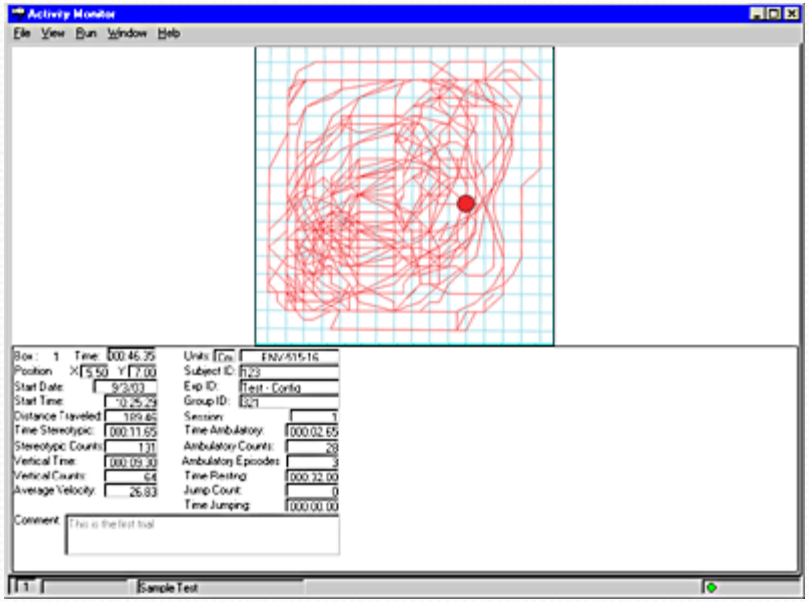
Ανηδονία

Ελεγχος αντικαταθλιπτικής Δράσης

Πειραματικά μοντέλα – Πρότυπα - Μοντελοποίηση

Ψύχωση

Δράση αμφεραμίνης ?



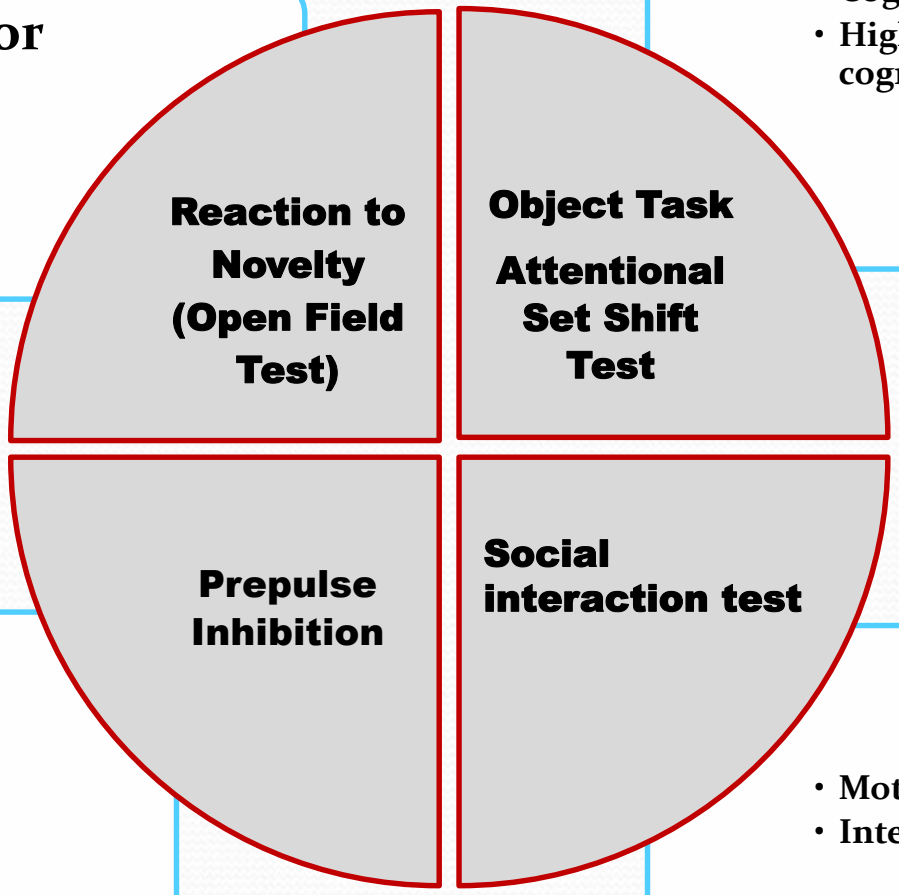
Πιθανή αντιψυχωσική Δράση

Πειραματικά μοντέλα – Πρότυπα - Μοντελοποίηση

Ψυχωση

- Psychomotor Effects

- Cognitive Effects
- Higher order cognitive Effects

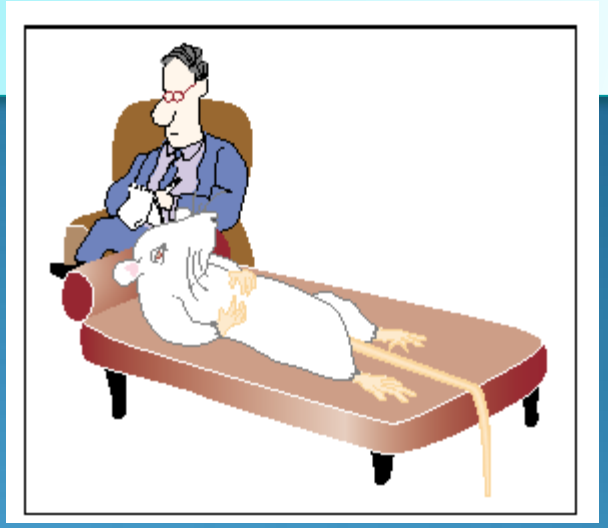


- Effects on sensorimototor gating – Filter out unnecessary information

- Motivation
- Interaction

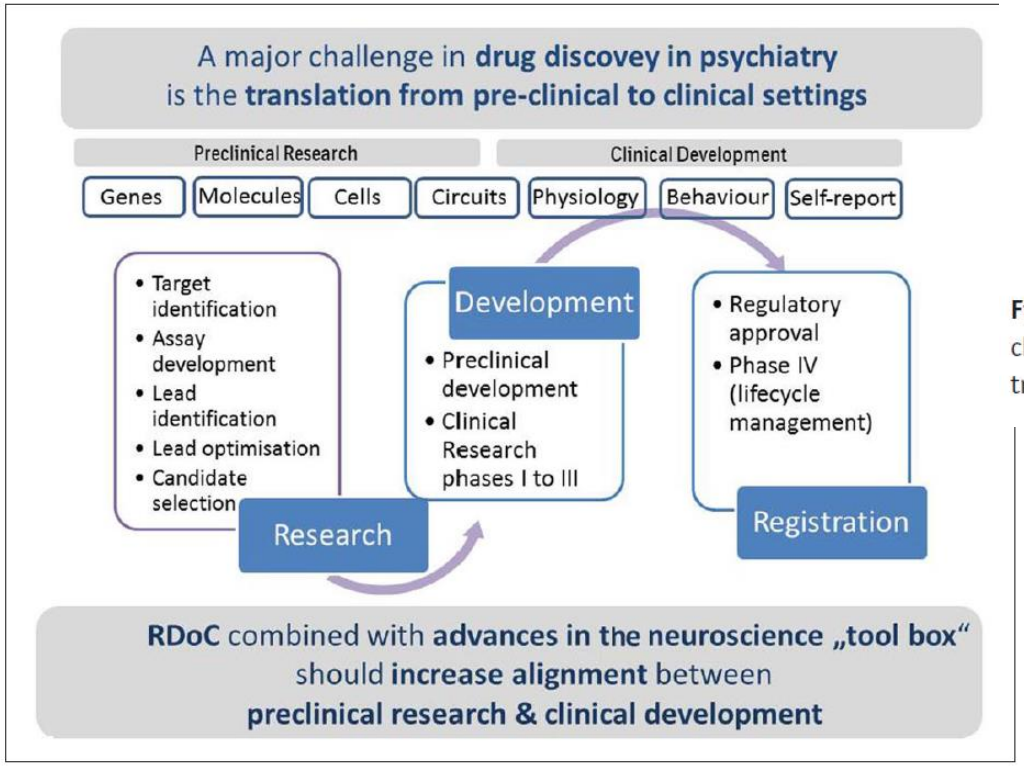
- Ιδανικό μοντέλο προσομοίωσης Διαταραχής ΚΝΣ?
- Προσέγγιση συμπτωματολογίας ?
- Συσχέτιση με Νευροβιολογικό Υπόστρωμα
- Φαινότυπος - Ενδοφαινότυπος – Μικροφαινότυπος

- **Απαρτίωση προσεγγίσεων**



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

Ερωτήματα προς συζήτηση - Προοπτικές



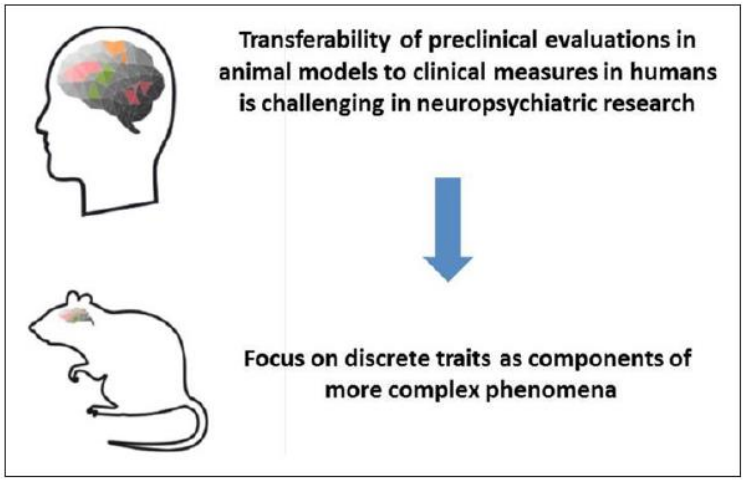


Figure 2. The complexity of the human brain and behaviour poses a challenge to neuropsychiatric drug development. Focus on discrete traits as components of more complex phenomena.

*** Research domain criteria (RDoC)**

Nicholson and Somer, 2018
Brain and Neurosciece Advances

Ερωτήματα προς συζήτηση - Προοπτικές

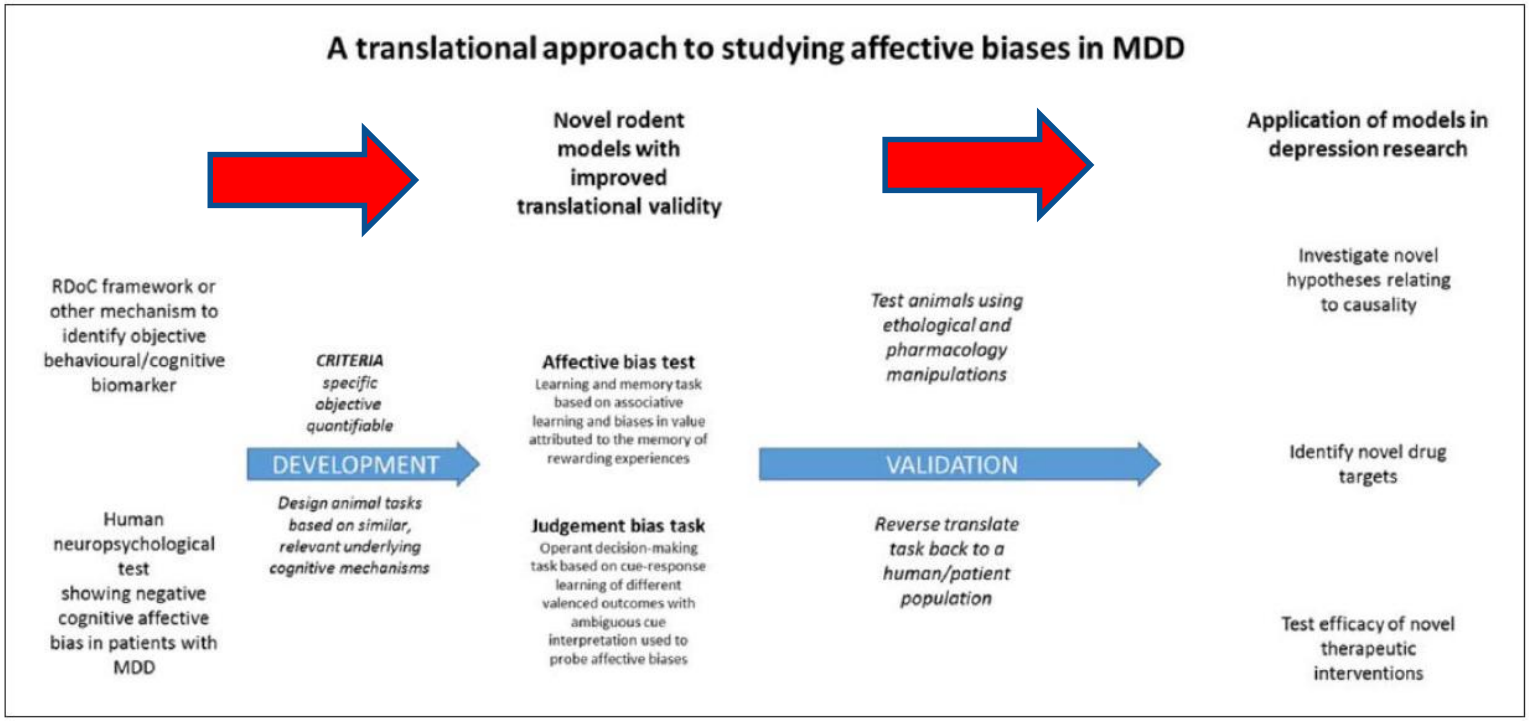


Figure 2. Overview of an approach to develop better translational behavioural methods to study relevant neuropsychological characteristics of psychiatric disorders and improve integration of fundamental biology, preclinical drug discovery and development, and clinical studies. See also discussion in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

Robinson, 2018,
Brain and Neurosciece Advances

Ερωτήματα προς συζήτηση - Προοπτικές

Sex differences in hypothalamic-pituitary-adrenal ax is: 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.

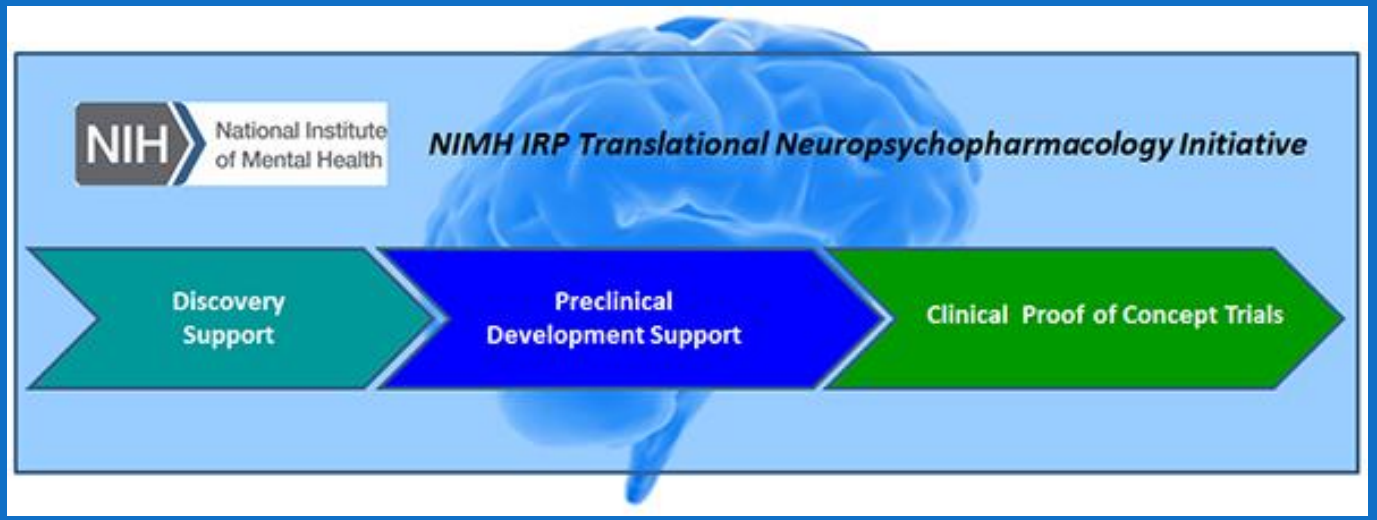
The main theme is to develop a new paradigm for drug discovery that questions the claim that animal models or assays fail adequately to predict Phase 3 clinical trials.

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.

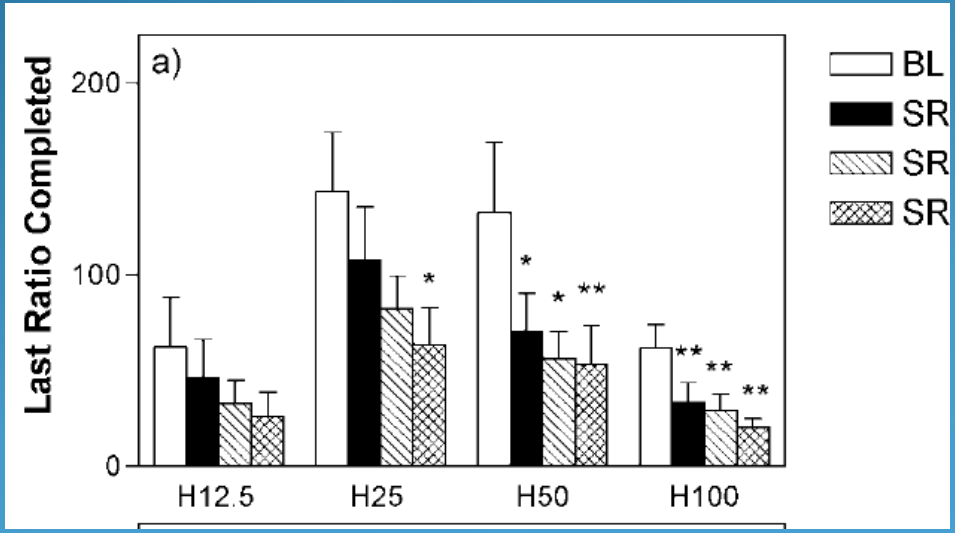
Translational Neuropsychopharmacology Task Force (TNTF).

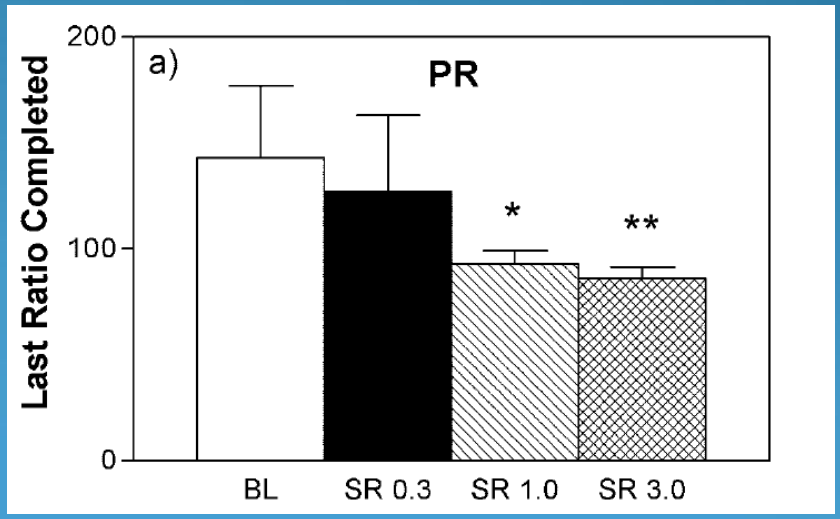


Παρουσίαση αποτελεσμάτων
Συμπεράσματα

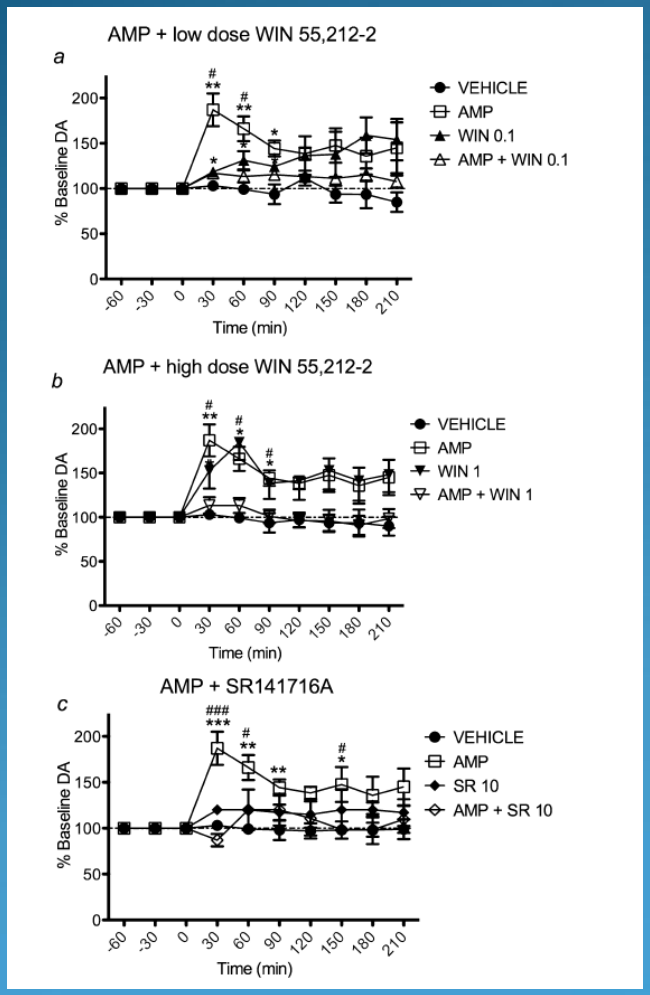
Παρουσίαση αποτελεσμάτων
Συμπεράσματα

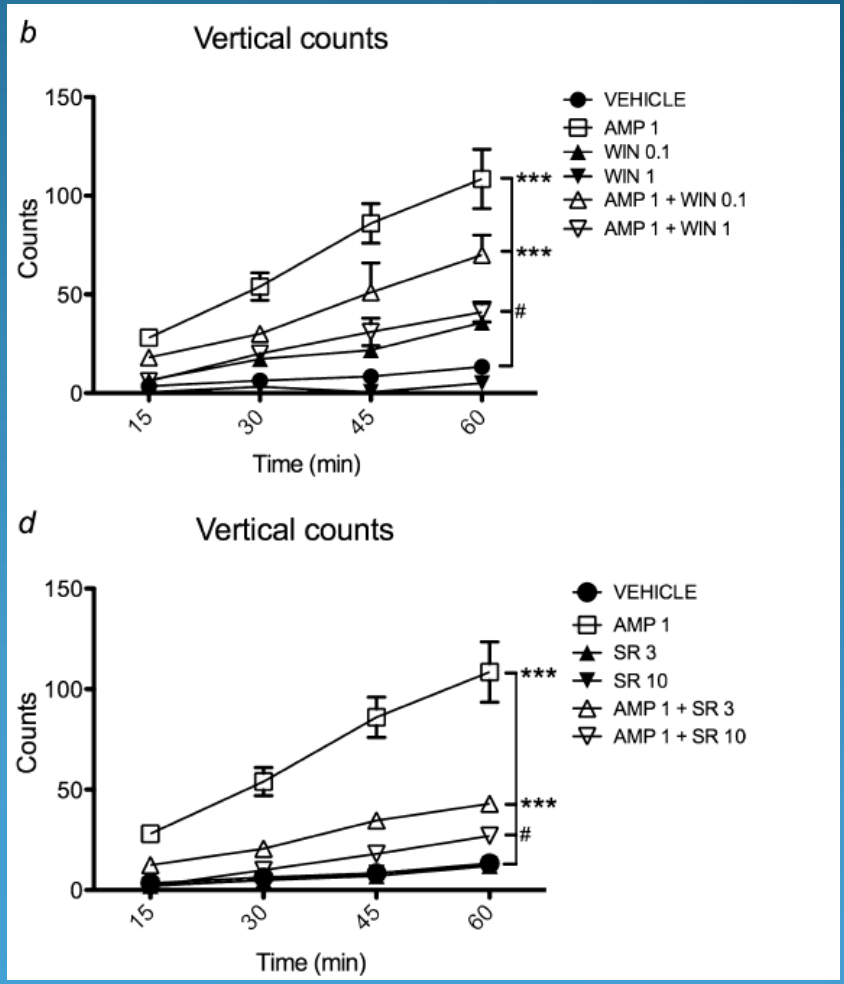
J Pharmacol Exp Ther. 2003 The cannabinoid CB1 antagonist N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl) -4-methylpyrazole-3-carboxamide (SR-141716A) differentially alters the reinforcing effects of heroin under continuous reinforcement, fixed ratio, and progressive ratio schedules of drug self-administration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



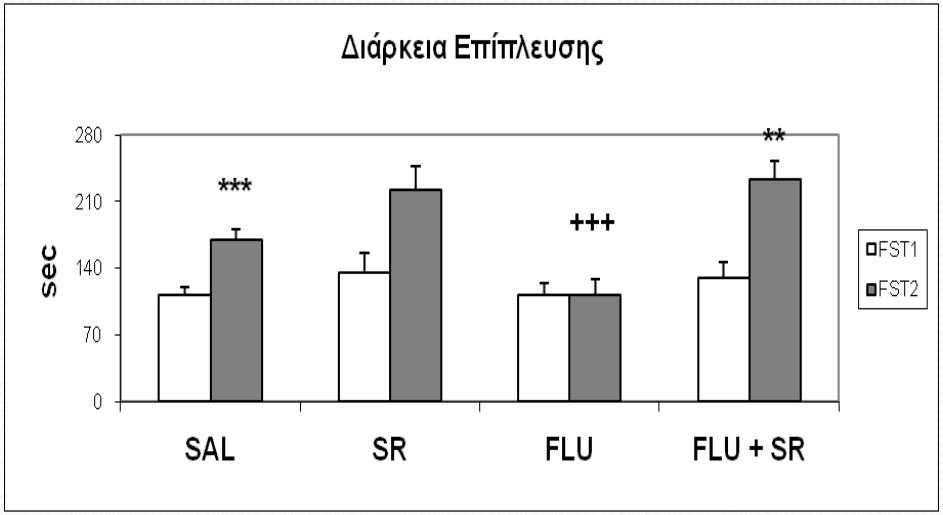


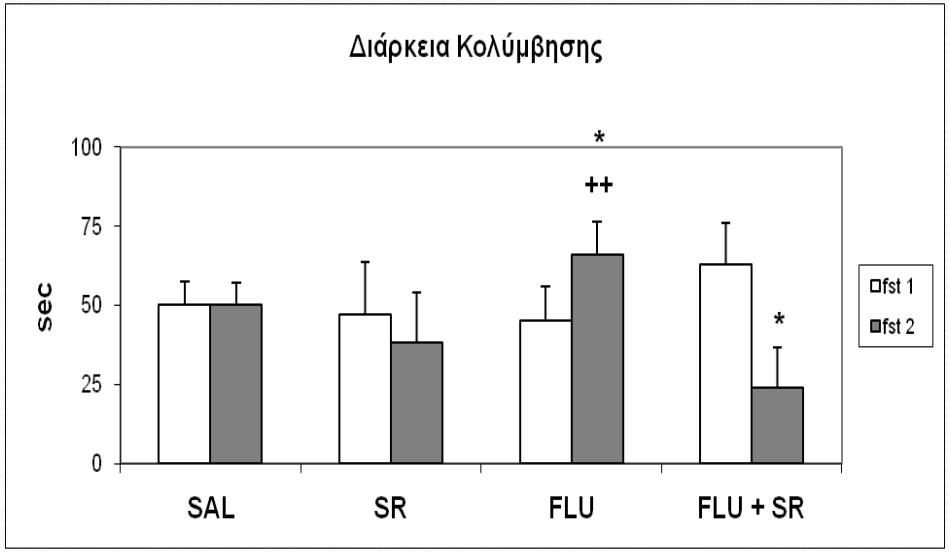
Polissidis et al,. Cannabinoids negatively modulate striatal glutamate and dopamine release and behavioural output of acute D-amphetamine. Behav Brain Res. 2014





ΑΛΛΑ?



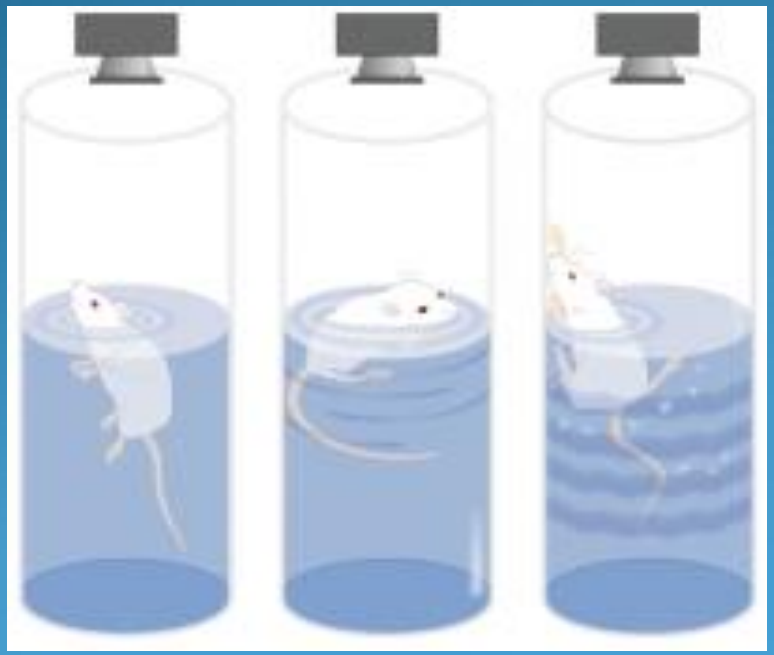


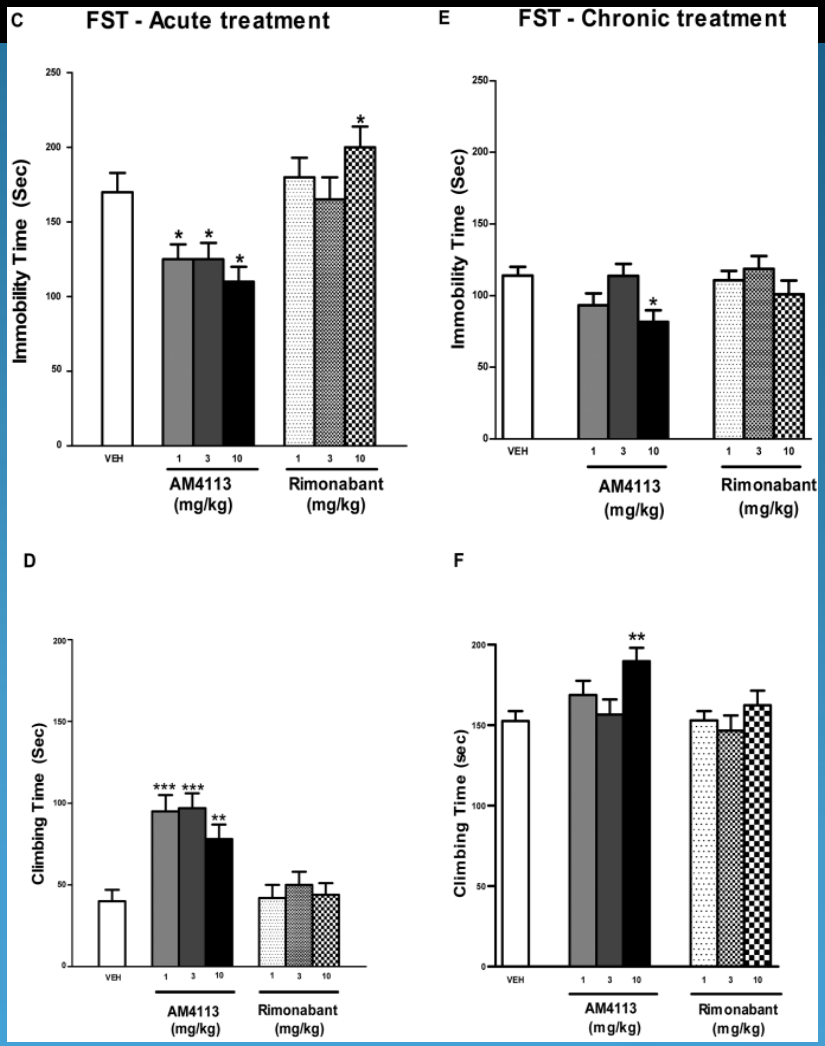
*** p<0.001,
**p<0.01,
* p<0.05 για στατιστικά σημαντικές διαφορές μεταξύ πρώτης και δεύτερης δοκιμασίας εξαναγκασμένης κολύμβησης.

+++ 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[1], Delis F, Antoniou K, Loureiro M, Laviolette SR, Vemuri K, Makriyannis A, Le Foll B.





Problems and crisis in Preclinical research ?

Reproducibily 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

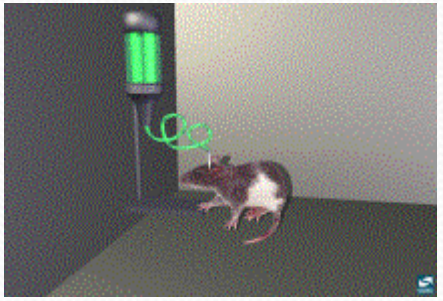
Μετά από 1h

Testing Phase

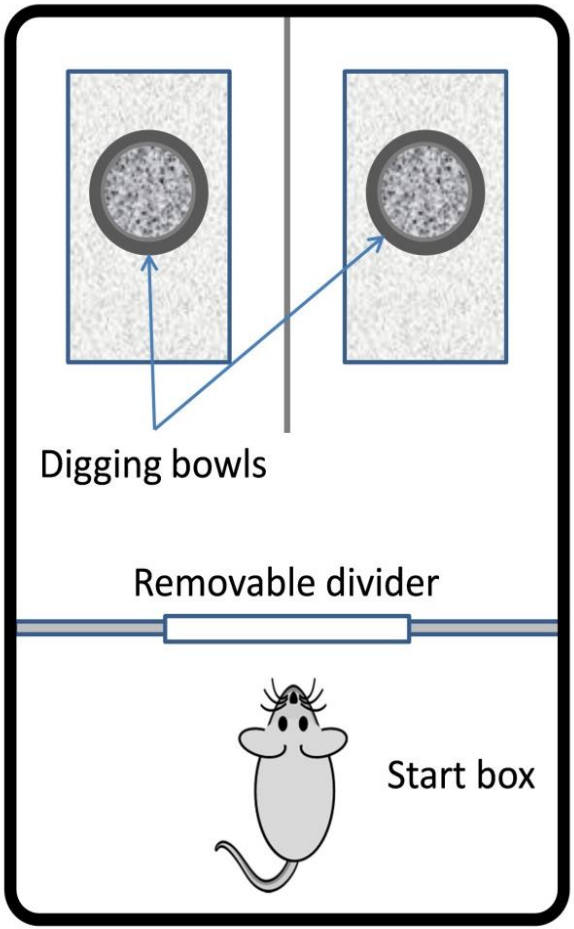
T2= 3min

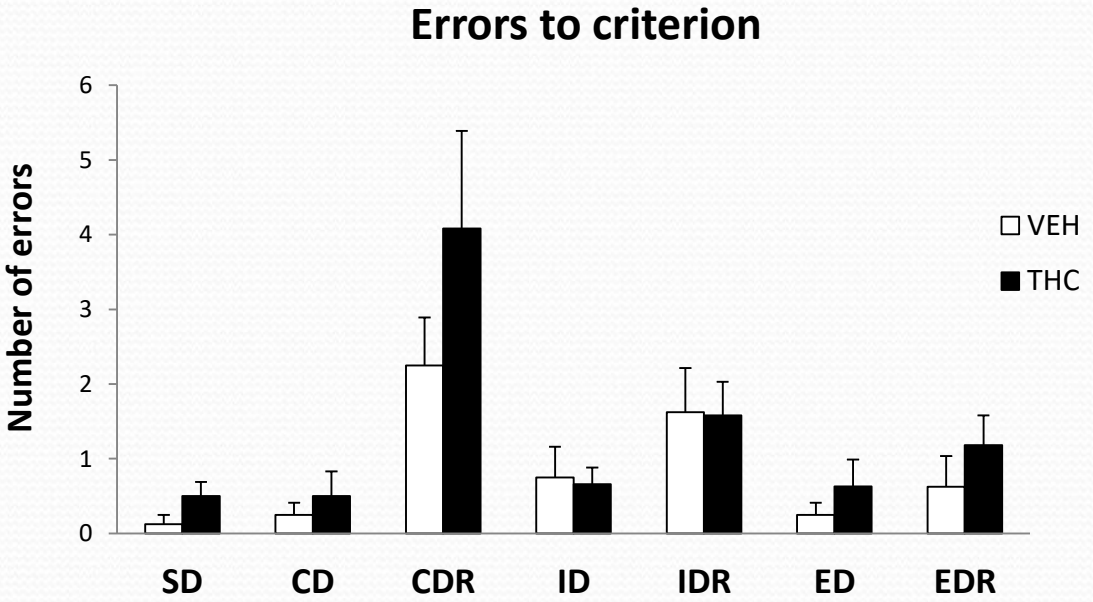
F

N



Μη επίδραση στις ανώτερες εκτελεστικές λειτουργίες





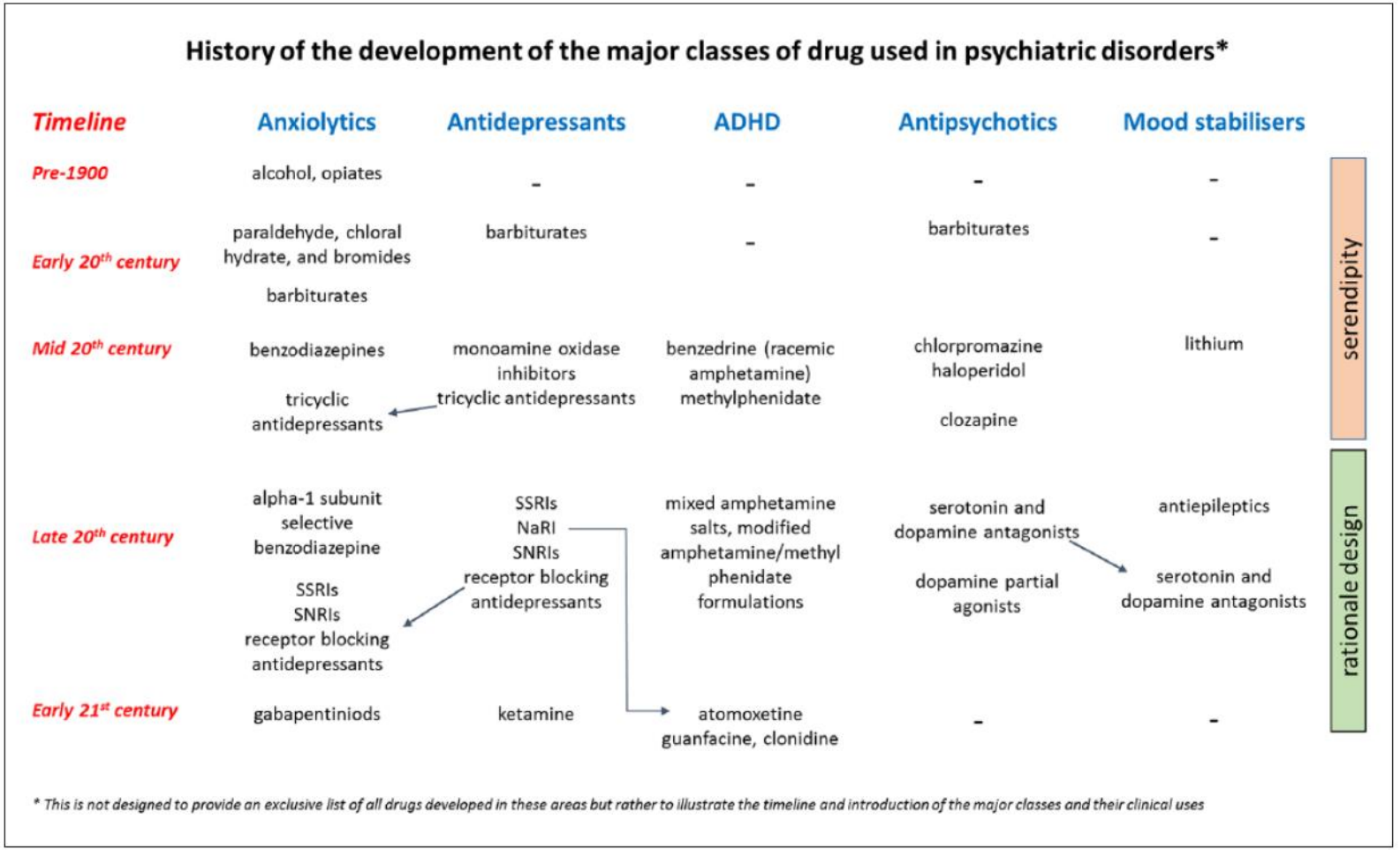
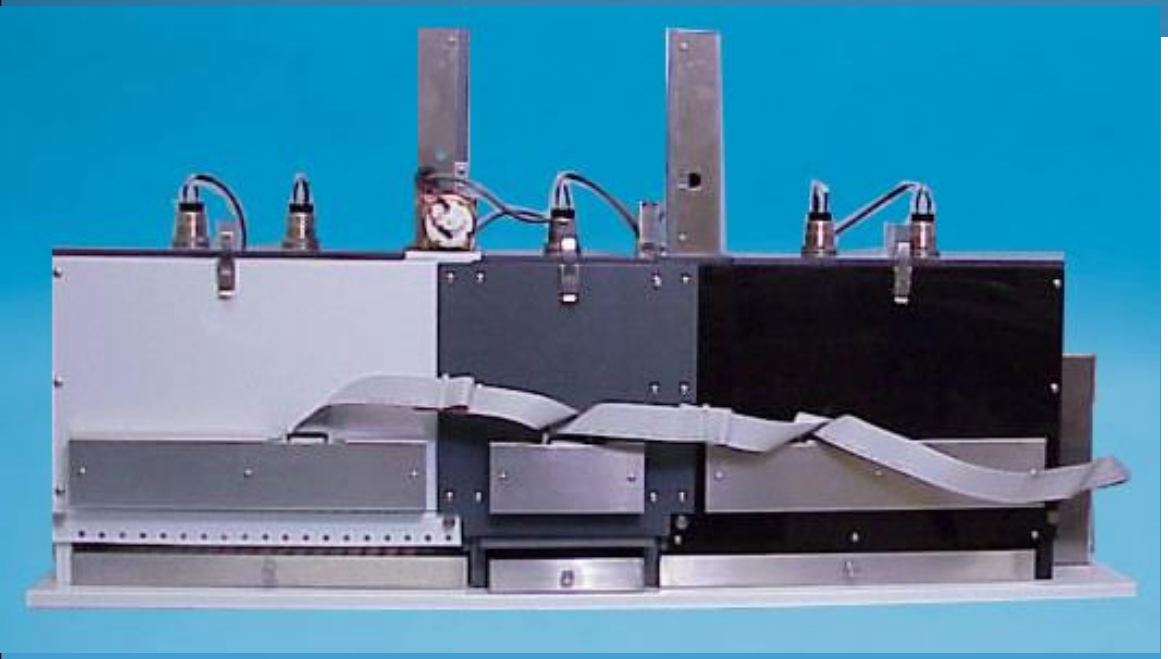


Figure 1. Drugs have been used to modify behaviour throughout humanity; however, the clinical use of drugs for specific conditions really developed from the start of the 20th century. This overview illustrates the timeline associated with the major classes of drugs used to treat psychiatric disorders. 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.



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