

CNS safety biomarkers in humans and their application in early-phase clinical drug development

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CNS drug development failure

- what leads to CNS side effects?

NeuroCart®

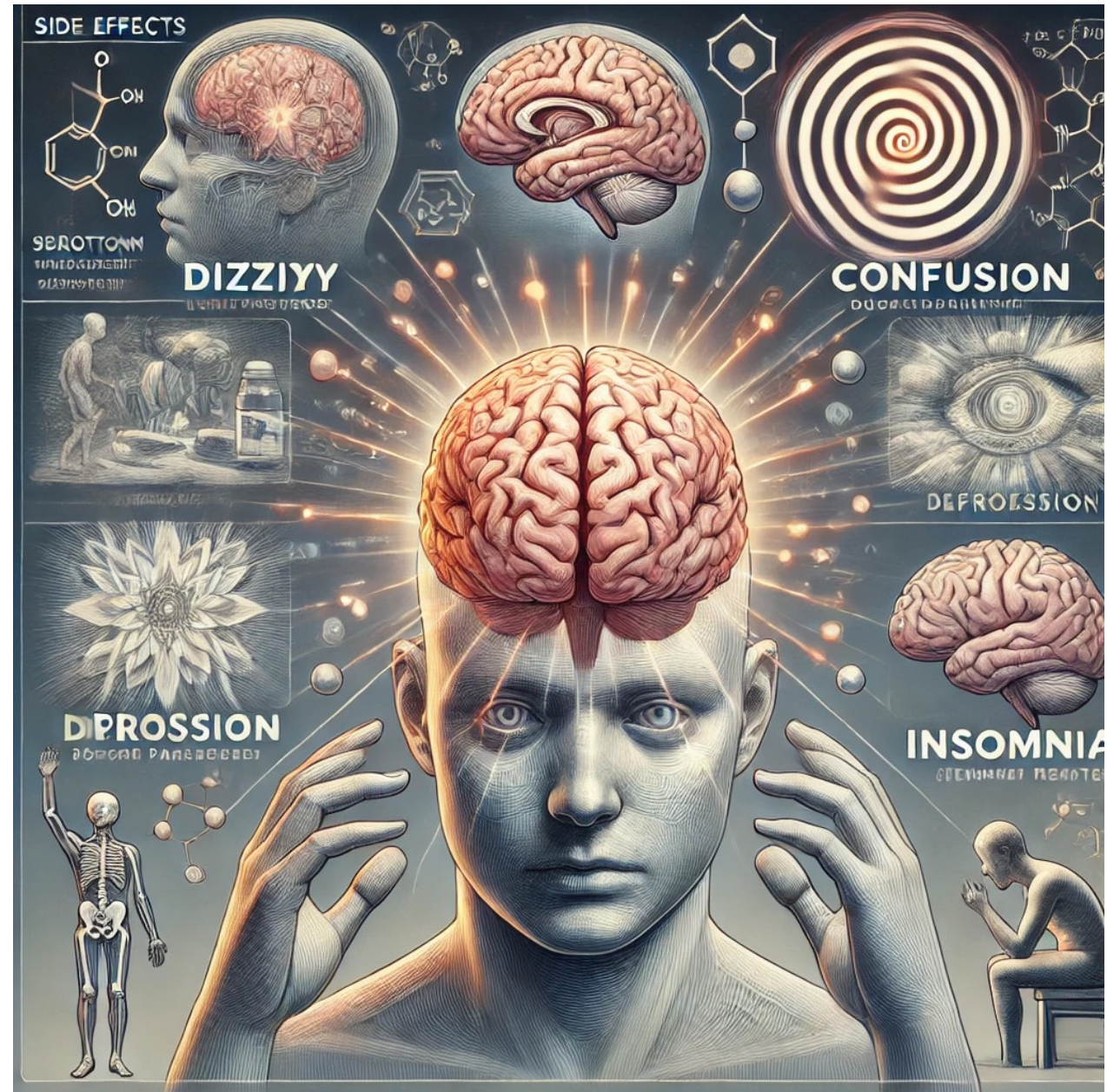
- CNS drug responsive domains
- multidimensional components

Case

- NR2B NAM

Future

- NeuroKit®



CNS Drug Development Failure Due to Side Effects

High Overall Failure Rates for CNS Drugs

- CNS drug development faces some of the highest failure rates in the pharmaceutical industry; only about **8–15%** of CNS drug candidates eventually reach the market.

Role of Side Effects and Toxicity

- Across all drug development, about **30%** of failures are attributed to unmanageable toxicity or unexpected side effects.
- For CNS drugs specifically, side effects are **critical**, as the **CNS controls behavior and cognition**.
- Even non-life-threatening neurological or behavioral side effects are **often deemed unacceptable** and can lead to the discontinuation of a drug's development.

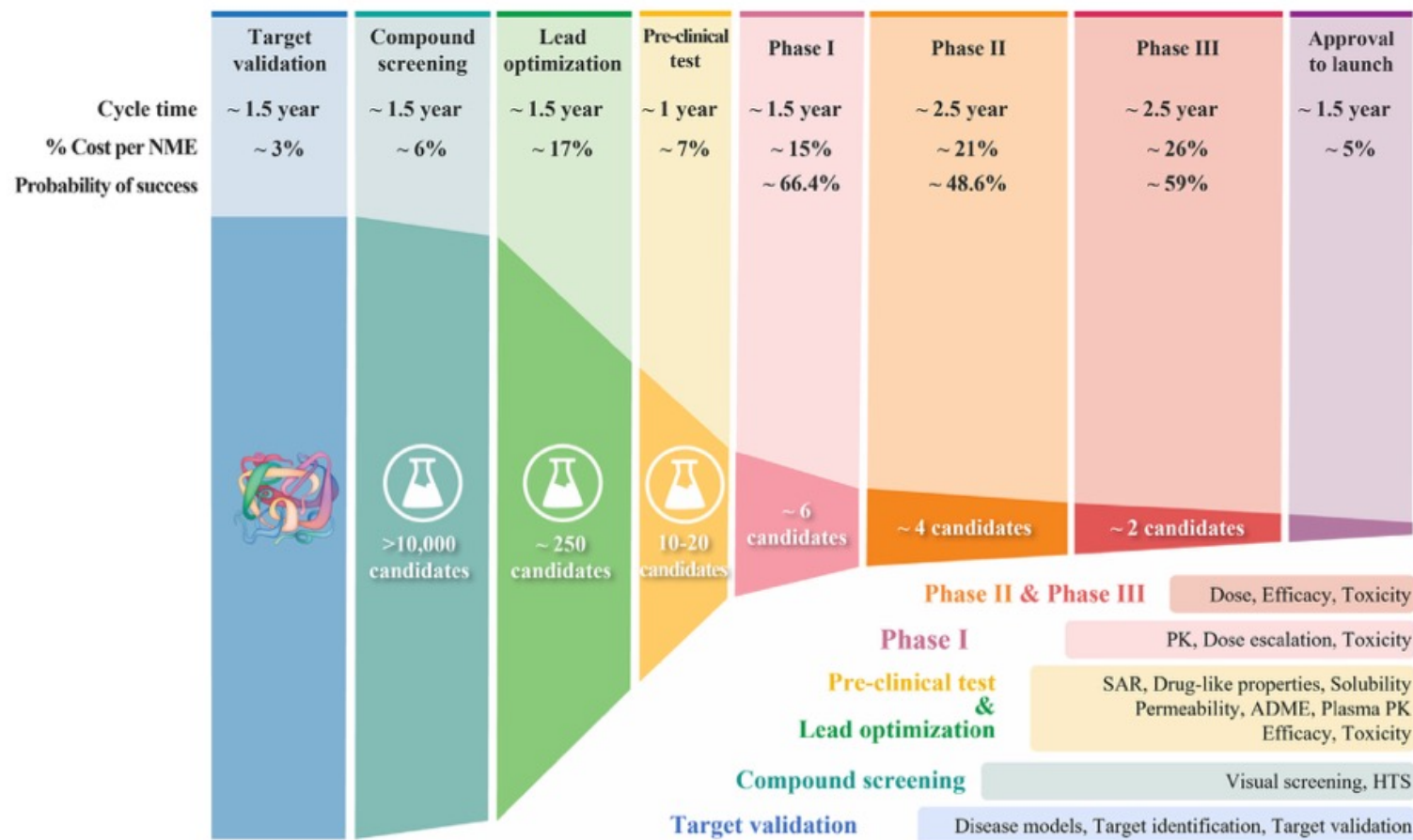


Figure 1 The process of drug discovery and development, and the failure rate at each step.

Why do CNS drugs lead to more side effects?

- **CNS drugs have to be able to pass the blood-brain-barrier so are often smaller and (relatively) lipophilic**
- **Because of this, they are often**
 - highly protein bound
 - and undergo CYP450 mediated (phase 1) metabolism leading to many weird metabolites
- **This leads to more on-target side effects:**
 - Protein bound drugs have higher chance of side effects due to prolonged drug effects, population differences in protein levels, interactions with foods and drugs
 - Lipophilic drugs accumulate in lipid tissues leading to prolonged drug effects and population differences in adipose tissue and V_d
 - CYP450 mediated metabolism can become saturated leading to non-linear pharmacokinetics at higher concentrations
- **And to more off-target side effects:**
 - CYP450-based metabolic variations can lead to aberrant metabolites leading to drug allergies (skin rash) and idiosyncratic reactions (bone marrow depression, hepatic failure)
 - Lipophilicity leads to membrane destabilisation causing teratogenicity and genotoxicity
 - Lipophilicity can affect membrane conductivity leading to cardiac arrhythmias and QT-prolongation



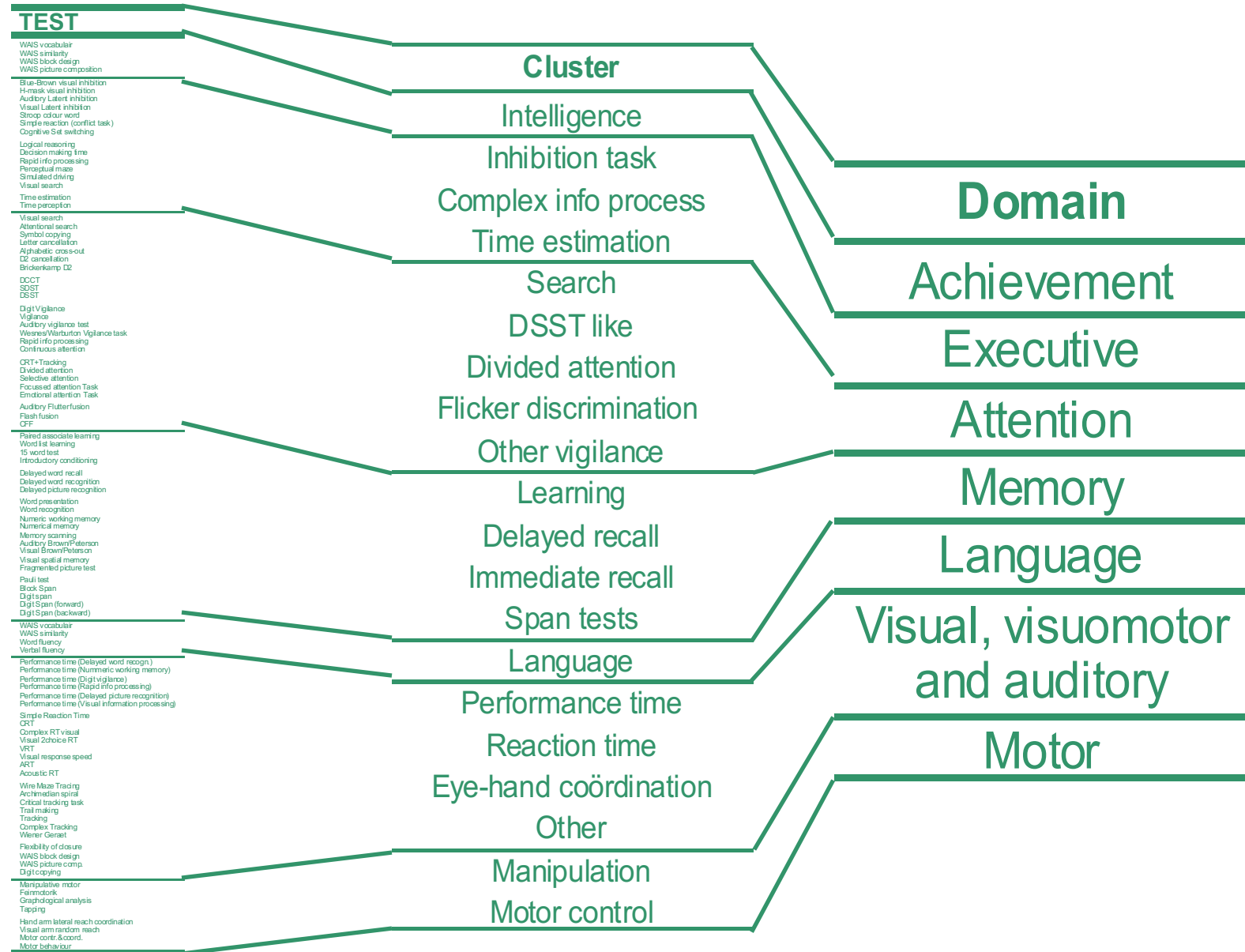
The Centre for Human Drug Research

- Based in Leiden, the Netherlands
- An independent institute specialising in innovative early-stage clinical drug research



NeuroCart®





Selection of drug sensitive pharmacodynamic CNS-biomarkers

Proper test requirements

- repeatable (6-10 times)
- limited version/learning effects
- reproducible

No impact on phase 1 study requirements

- sensitive in small groups
- (semi)-automated: < 24h reports)
- unaffected timelines
- 'value-for-money'

Well-established

- consistent results across studies (>50%)
- sufficient experience (N>10)

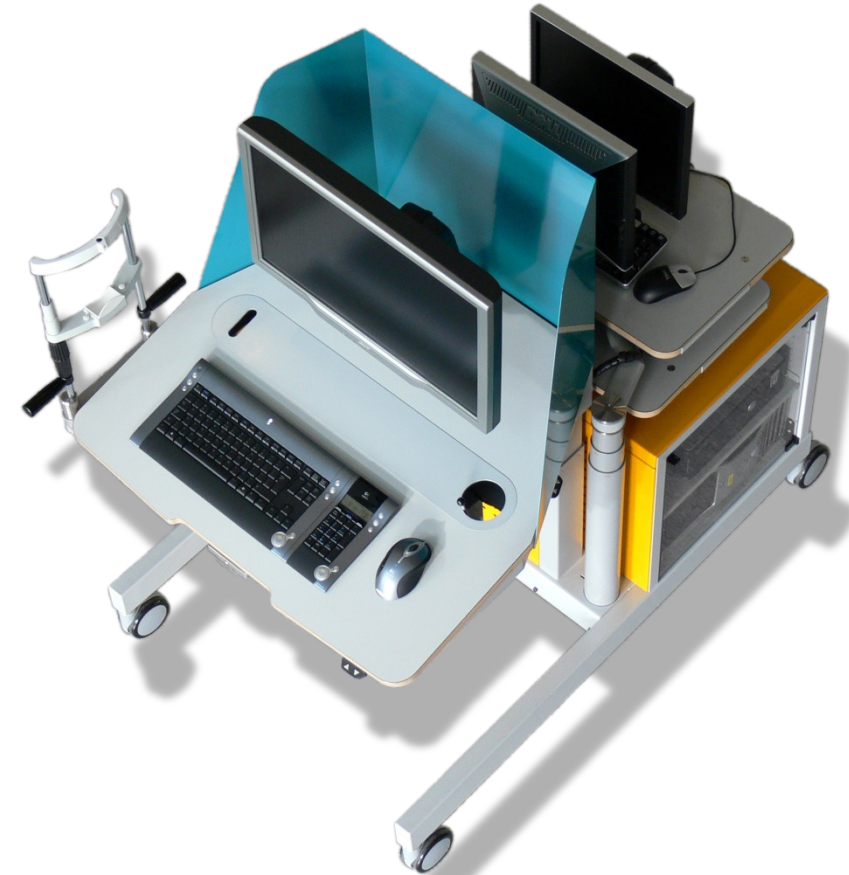
Drug-responsiveness

- sensitive to low therapeutic doses
- dose-response relationships

Wide range of drug-responsive domains

Core Components of NeuroCart®: a flexible, multimodal CNS test battery

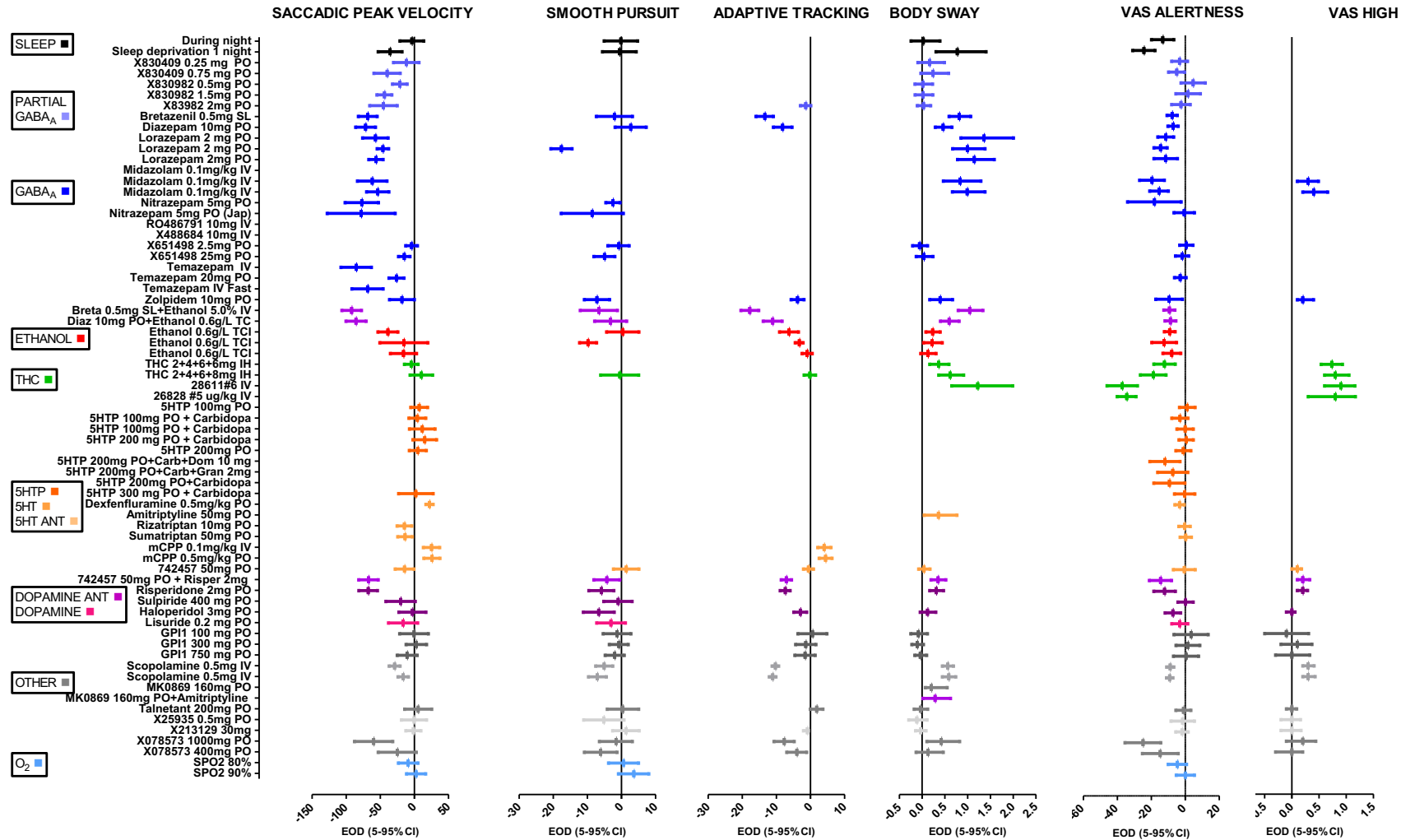
- Saccadic eye movement 2'
 - Smooth pursuit eye movement 2'
 - Memory testing
 - N-back working memory test 3'
 - VVLT immediate/delayed word recall/recognition 20'+15'
 - Milner maze spatial learning 8'
 - Adaptive tracking 3'
 - Finger tapping 2'
 - Body sway 2'
 - Visual analogue scales 2'
 - Pharmacology-EEG 2'
-
- Total 18 – 40'



NeuroCart®

NeuroCart® Meta-Analysis of 100+ Drugs

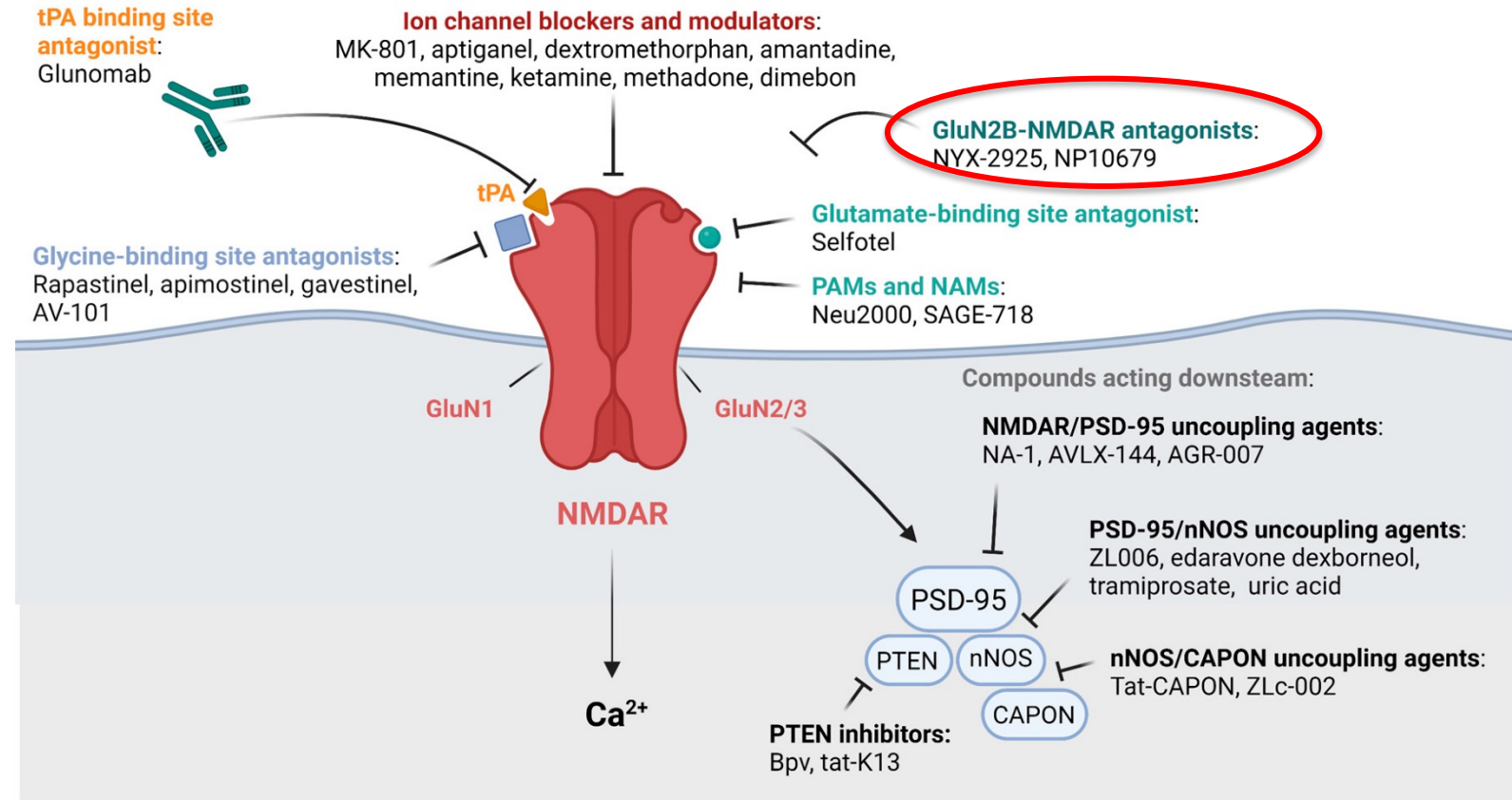
profiling of CNS-active drugs and tests



Case

NMDAR subtype selective compounds

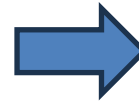
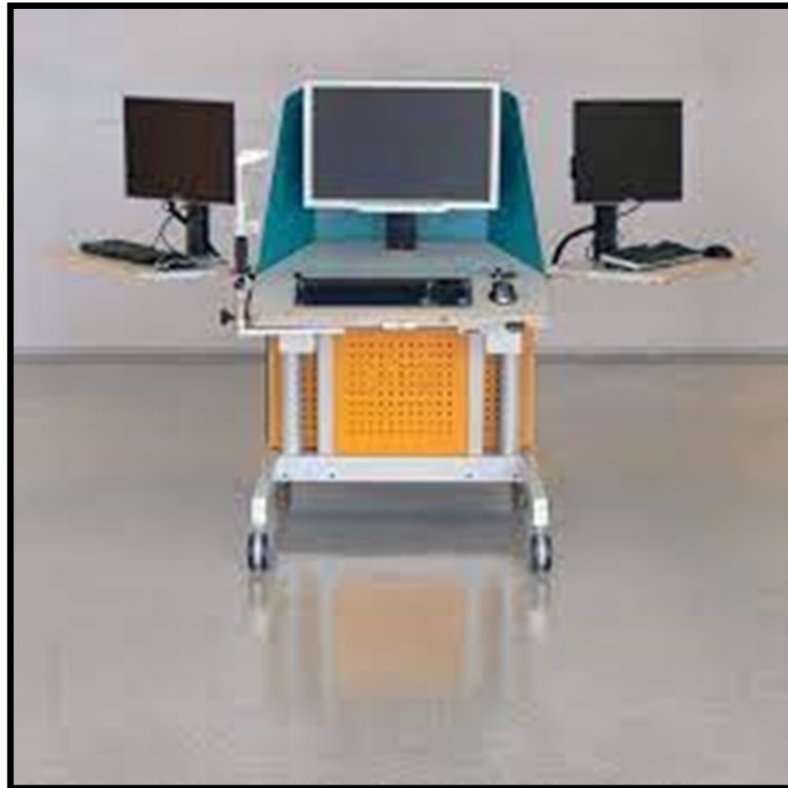
- **Ketamine** binds equally to NR2A and NR2B subunit containing NMDA-R
- Effects on cognition and perception are more NR2A mediated
- Both ketamine and NR2B NAMs induce rapid, long-lasting synaptic potentiation in reward-related circuits, persisting after drug elimination, correlating with sustained antidepressant responses in patients with MDD
- NR2B selectivity expected to lead to fewer side effects



Future

From NeuroCart[®] to NeuroKit[®]

NeuroCart



NeuroKit



NeuroKit tests

1. Saccadic Eye movement
2. Smooth Pursuit Eye movement
3. Adaptive Tracking
4. Body Sway
5. N-back
6. Finger tapping
7. Visual Analogue Scales



Varjo XR-4

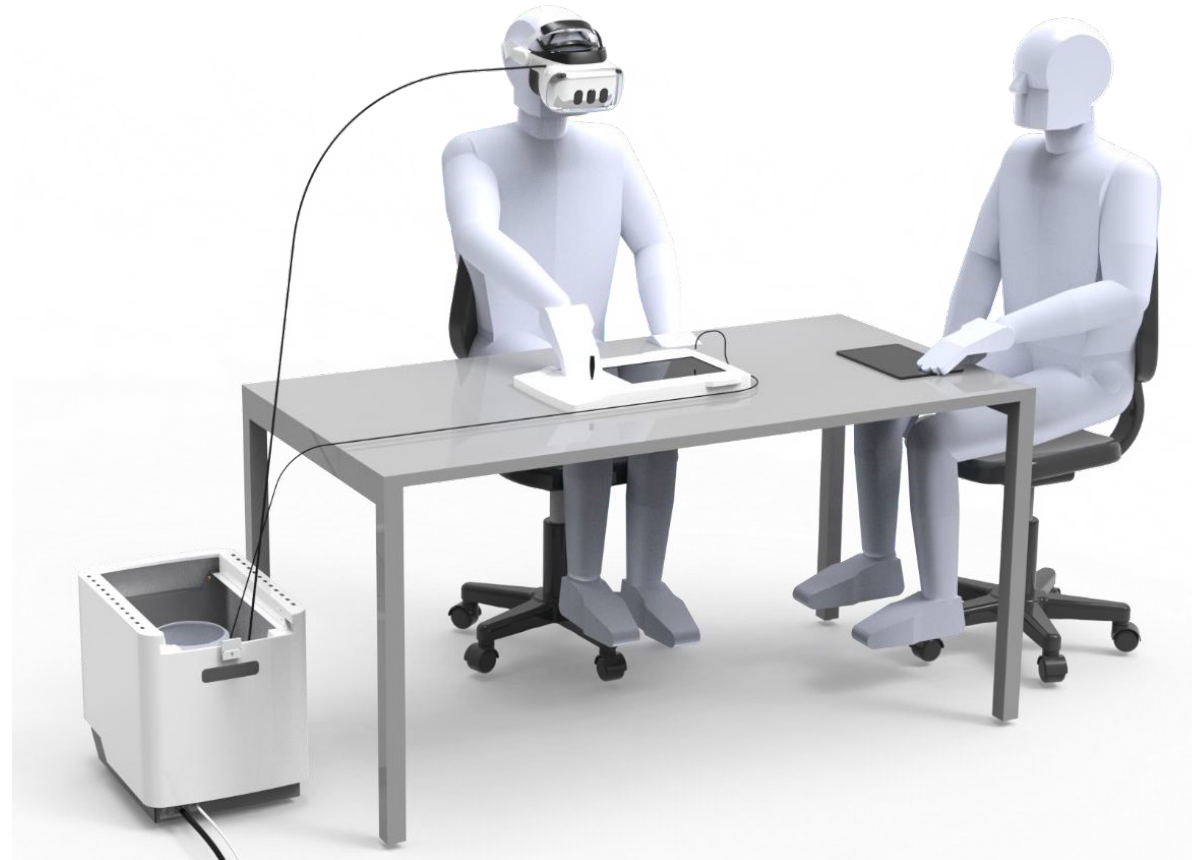


Movella Dot

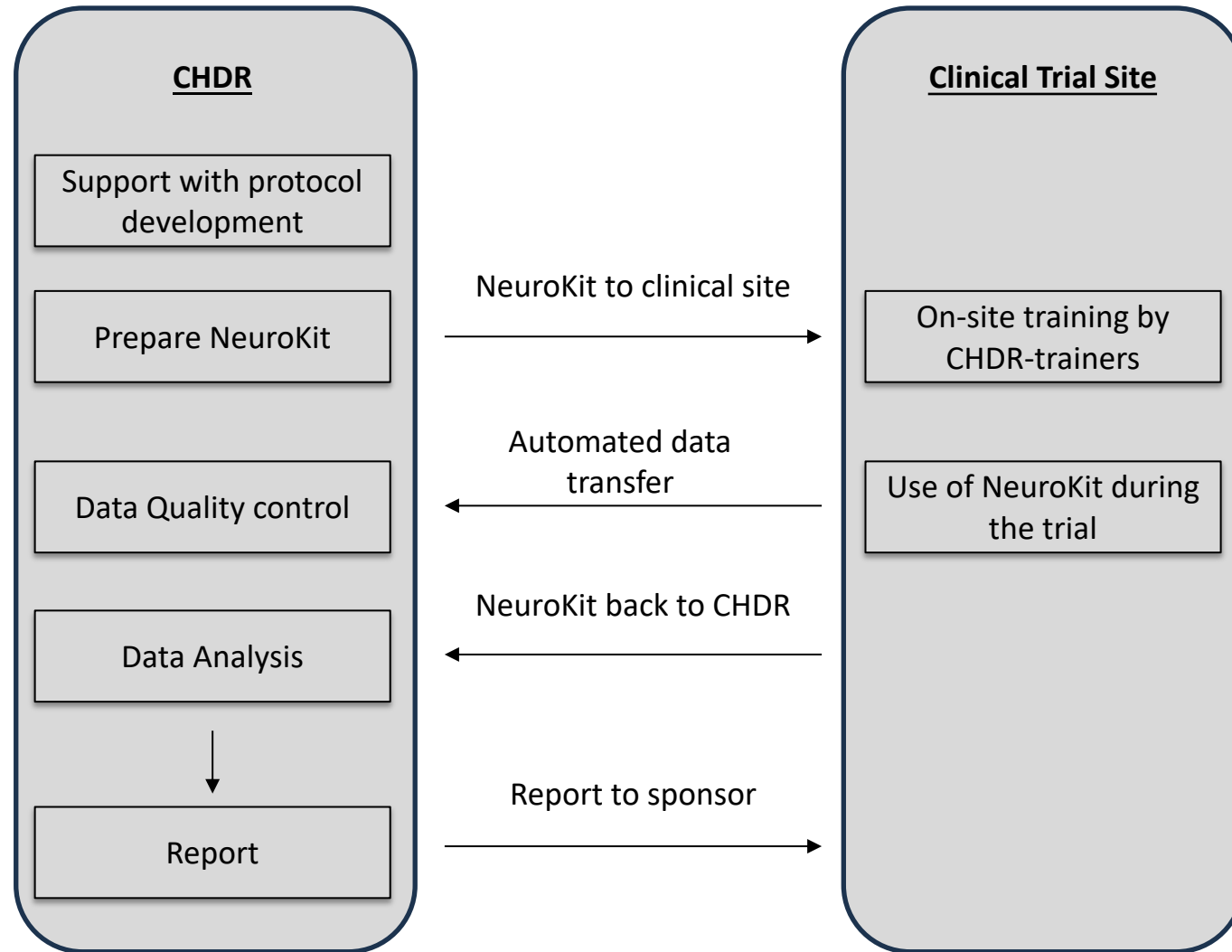


Samsung Galaxy Tab S9

NeuroKit – Visualisation



Product / Service





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Most Frequently Used Tests Within Drug-Sensitive Domains

Domain	Cluster	Sensitivity ↓	↑	Test
Executive	Inhibition	50%	62%	go-no go, Stroop, prepulse inhibition
	Info Processing	43% / 67%	39%	simulated driving, card sorting, arithmetic
	Time Estimation	17% / 43%		time estimation
Memory	Memory Span	40% / 55%		Sternberg, digit span, n-back
	Learning	38% / 60%		Word
	Immediate Recall		Spatial	
Attention	Delayed Recall			Picture
	Search	35% / 70%		letter cancellation, symbol copying, trail making
	DSST-like	43% / 66%		symbol-digit substitution
	Divided Attention	36% / 68%	71%	divided attention
	Flicker Discrimination	30% / 50%		critical flicker fusion
Visuomotor	Vigilance	13% / 42%	76%	continuous performance task
	Reaction Time	46% / 56%	50%	simple /complex reaction time
	Eye-Hand Coordination	41% / 78%		adaptive tracking, pursuit rotor, spiral tracing
Motor	Manipulation	33% / 76%	72%	Feinmotorik, finger tapping, pegboard
	Motor Control	58% / 85%	50%	Body Sway
Subjective	Alertness	36% / 79%	83%	VAS Bond & Lader, Von Zerssen Befindlichkeitsskala
	Mood	8% / 50%		profile-of-mood-scales
	Anxiety	28%		Spielberger trait anxiety index
	Drug Effect'	57%	96% / 98%	VAS Bowdle, VAS 'high', 'drug effect', addiction research center inventory