Can assessment of CNS target engagement help to minimize risk in early development.

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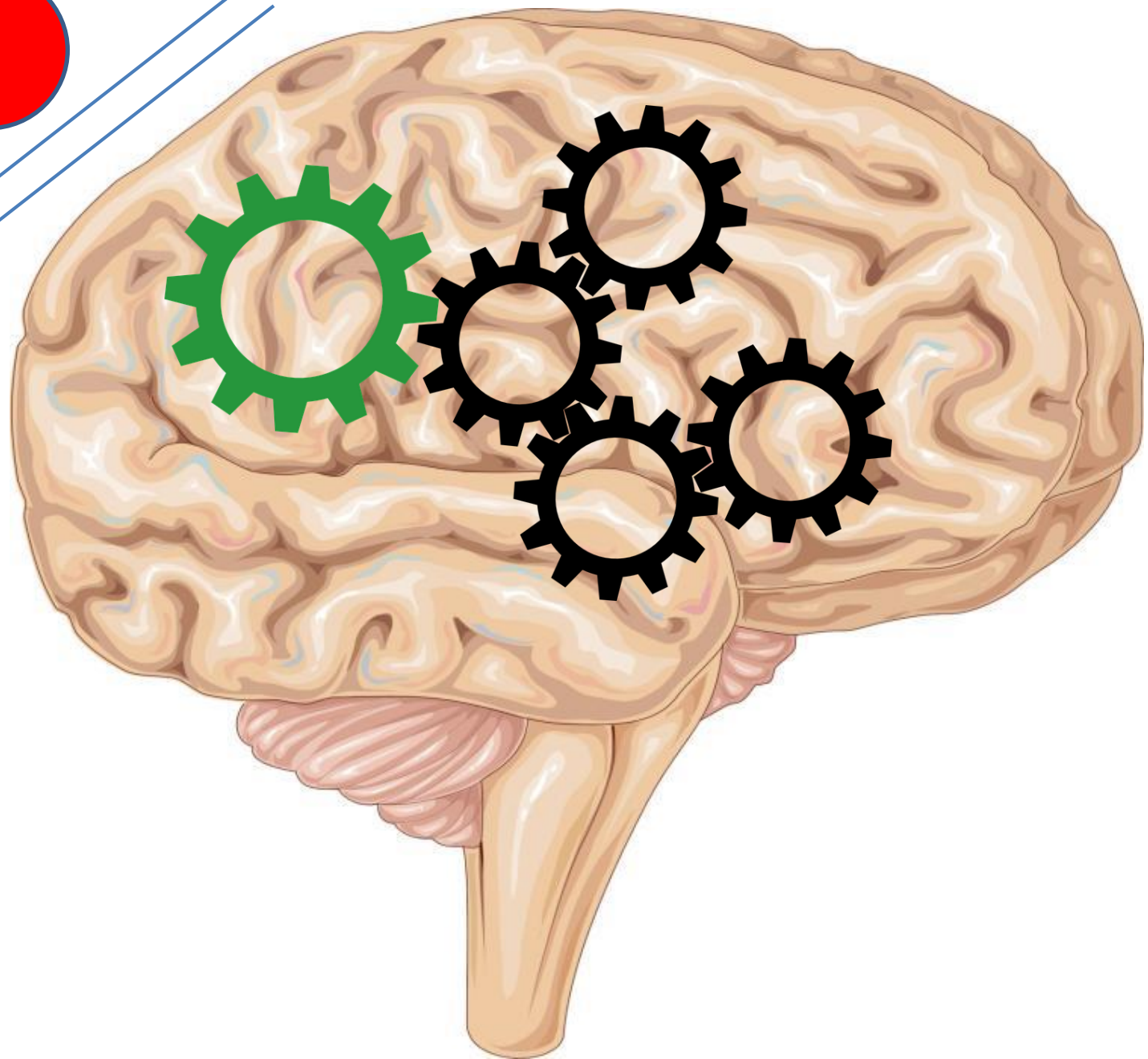
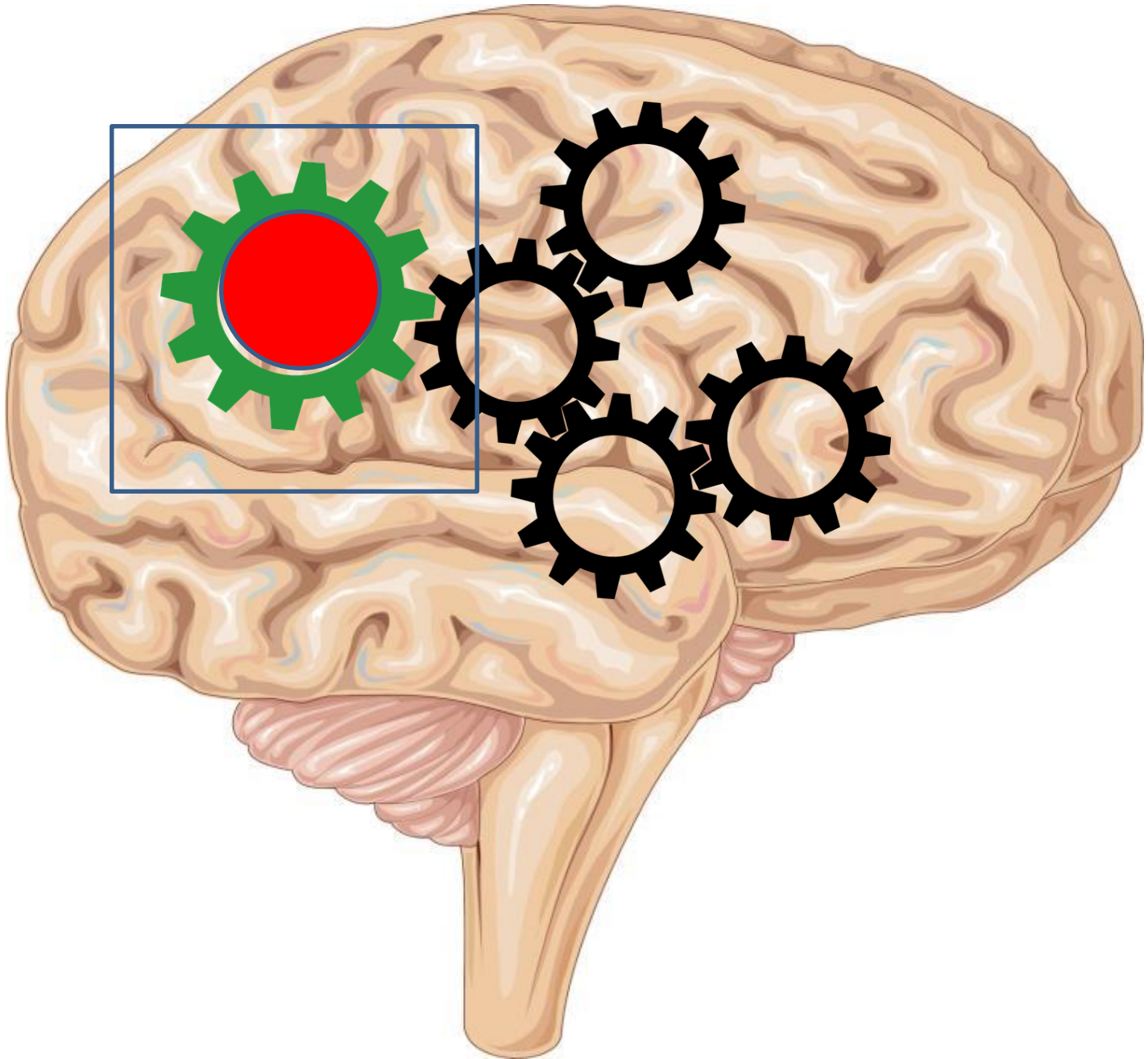
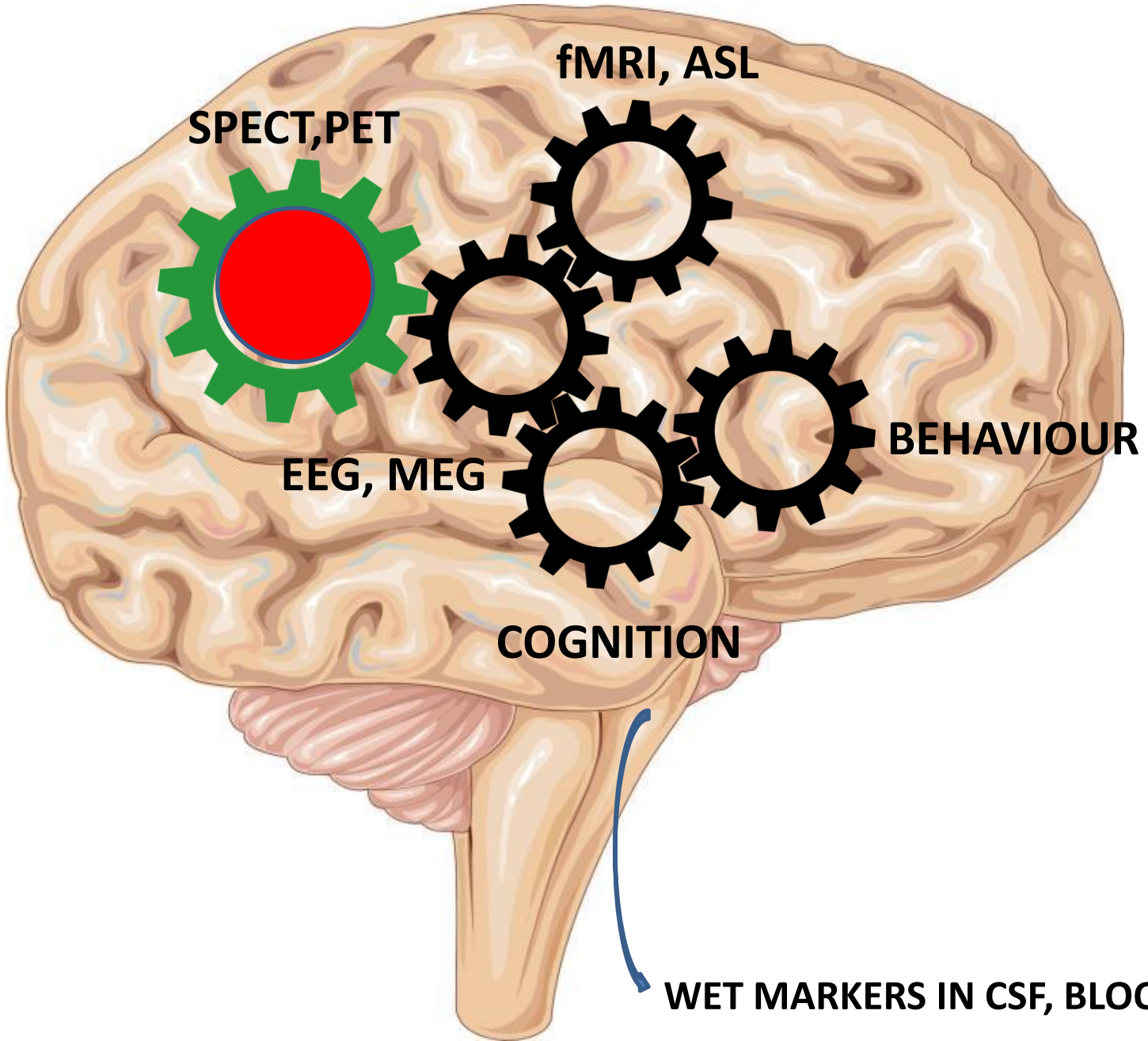
Blood to Brain Barrier






fMRI, ASL
SPECT,PET
EEG, MEG
BEHAVIOUR
COGNITION
WET MARKERS IN CSF, BLOOD?

Context of early Phase studies

- Generally first in Man
- Standardized study aiming to study and define:
  - Safety
  - Pharmacokinetics
  - Tolerability and AE profile
    - Define Maximum Tolerated Dose and/or safety margin
    - Define dose-limiting AEs
  - Pharmacodynamics (piggy backed) with no statistical power
  - Dose escalation between subjects with generally 6 under active and 2 under placebo

Very safe but not zero risk

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Main alternative options

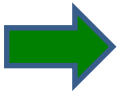
❶ Monitor **primary effect or target occupancy** associated with efficacy(molecular imaging):

- Impossible for first in class or relying on animal data only
- Human ligand availability, design and cost hurdles

❷ If not feasible, use a **decisionable biomarker**, **downstream** the MOA

- State of knowledge and validation hurdles

- Then add a **safety margin to go above it (4-X fold ?) for the real life of the drug**
  - registration (PK, genomic, DDI and TqT studies requiring a supratherapeutic exposure).
  - Dosing errors or overdose



Would limit probability of an off target activities

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Unrealistic option

- Do all in patients, « tolerability is different »
- In fact **hiding behind the fact that patients need the drug not healthy volunteers** and that legal aspects would differ
- With very rare exceptions it is not the safety & tolerability which is better it is the Risk/Benefit ratio which can speak away problems
- In many cases healthy subject tolerate better and surmount better an AE or toxic or exacerbated PD (adrenolytics, hypertension, liver toxicity etc..) than older, comedicated with multiple pathologies:
  - In the BIAL accident increase over the last 30 years of the « healthy age » from 35 to 50 allowed an undiagnosed comorbidity. *Younger better* ? *Not discussed by EMA*

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Progress ?

- Those who think « no Biomarker, no Drug » continued to do so for 15 years, not motivated by individual risk but more on the optimization of success rate;
- An innovative biotech that could not fund a PET ligand development or of a predictive wet marker and minimize costs;
- Middle of the road solutions between the usual way and an alternative way would start by a change of mindset.

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Progresses ?

How are we sure it is useful

We do not have the budget

We are not sure how Management will react to this change

- Middle of the road solutions would start by a **change of mindset**;

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Progresses ? 

- Possibly precompetitive consortia would be a way to share costs and research;
- Creating an ASL reference database may also pave the way to the future in a ligand-free, paradigm-free manner.

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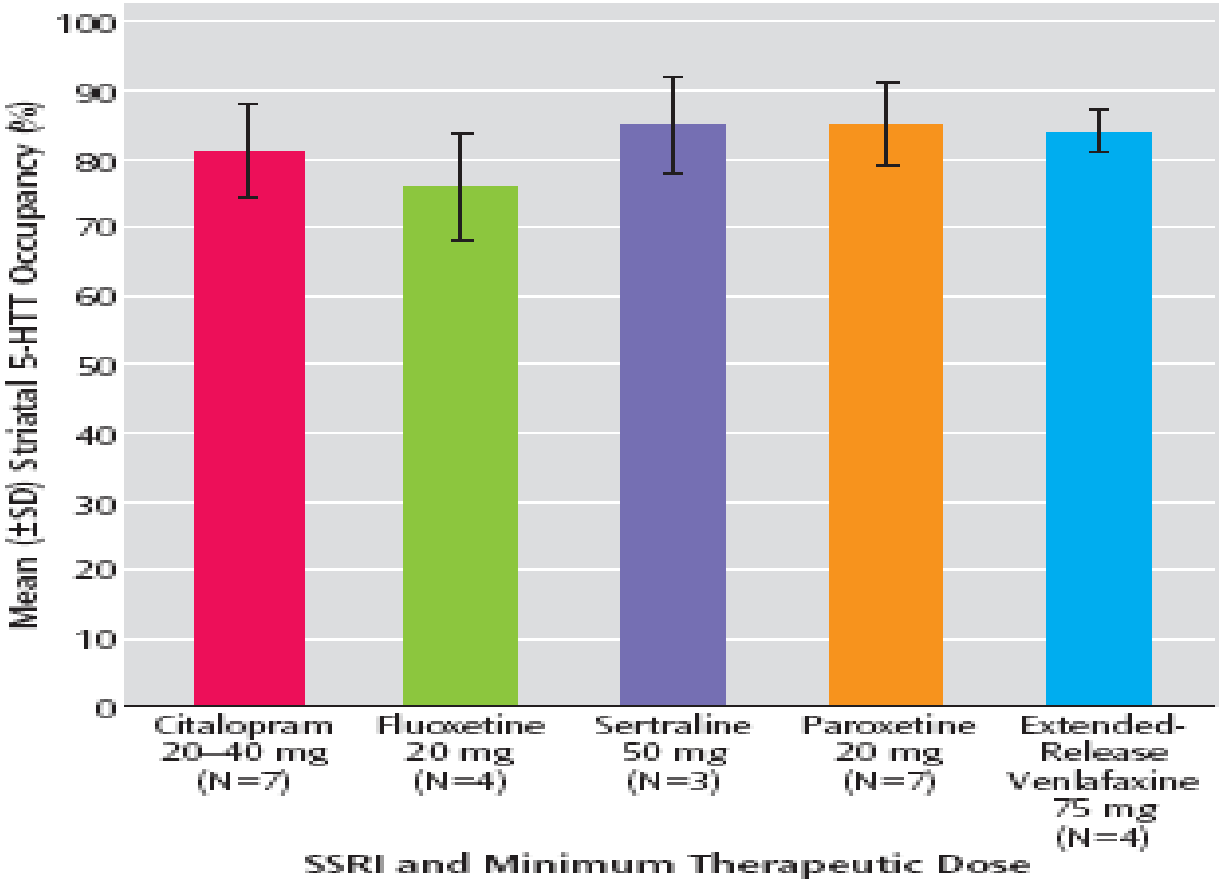
5HTTP PET occupancy at 4 weeks with 5 SSRIs

FIGURE 6. Striatal Serotonin Transporter (5-HTT) Occupancy in Depressed Subjects After 4 Weeks of Treatment at Minimum Therapeutic Doses of Five SSRIs



Form Meyer et al. 2004 Am J Psychiatry

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5HTTP PET occupancy at 4 weeks with 5 SSRIs

FIGURE 4. Relationship Between Striatal Serotonin Transporter (5-HTT) Occupancy and Dose or Plasma Concentration of Paroxetine in 14 Healthy and Depressed Subjects[a]

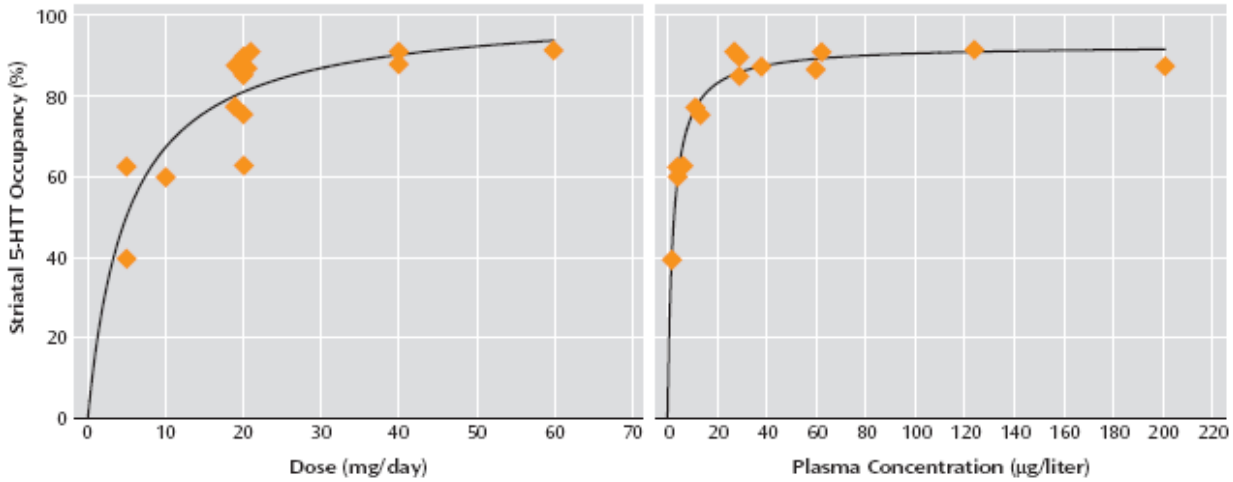

TABLE 1. Estimated Dose (ED_{50}) and Plasma Concentration (EC_{50}) Needed to Obtain 50% Serotonin Transporter Striatal Occupancy for Five SSRIs Administered to 77 Healthy and Depressed Subjects for 4 Weeks

SSRI	ED_{50} (mg/day)	EC_{50} (µg/liter)
Citalopram	3.4	11.7
Fluoxetine	2.7	14.8
Sertraline	9.1	1.1
Paroxetine	5.0	2.7
Extended-release venlafaxine	5.8	3.4

Meyer et al. 2004 Am J Psychiatry

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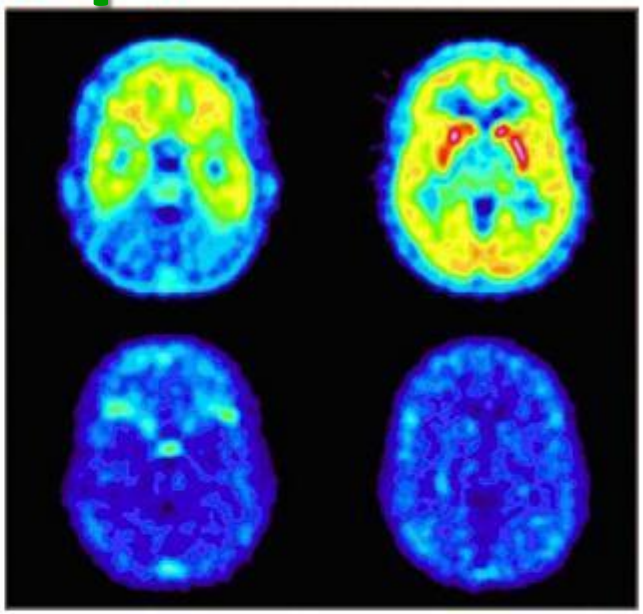
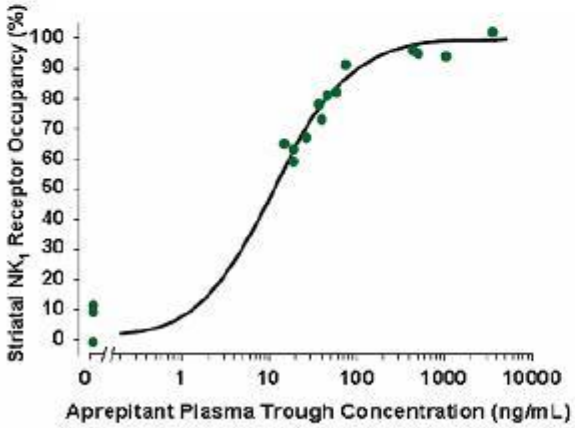
Example of successfull brain exposure-driven development

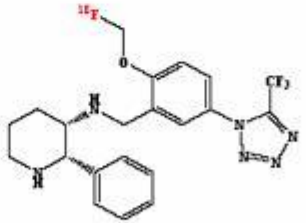
Aprepitant is a selective NK1 antagonist

Allowed full determination of plasma -Receptor occupancy in Humans

Was useful when Phase III trials in depression came back negative







[18F] SPA-RQ

Adapted from Bergstrom et al, Biol. Psych. 55, 1007 (2004)

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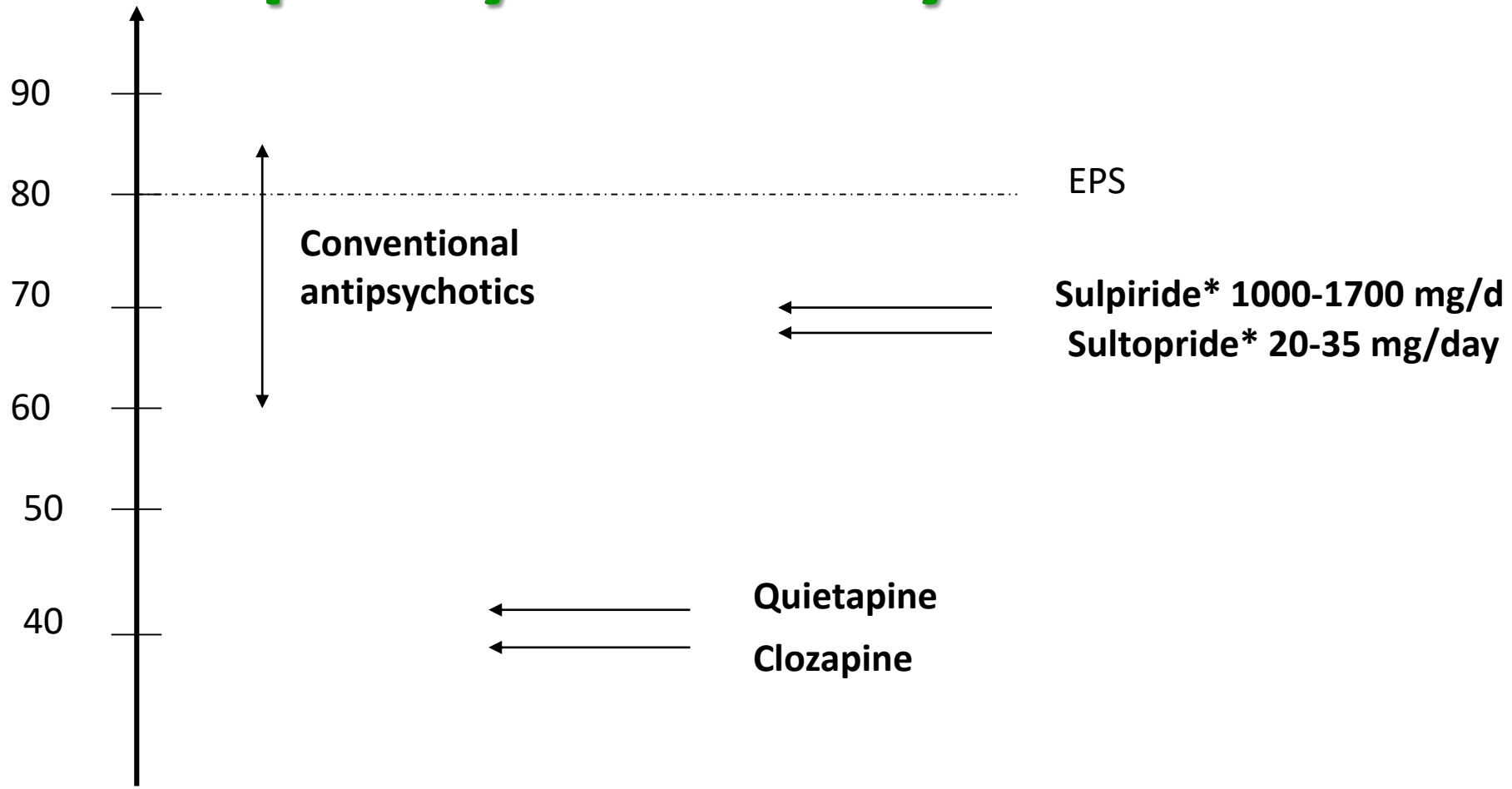
Dopamine D2 striatum occupancy at Steady-State



* From : Takano et al. 2006 Int J Neuropsychopharmacol

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Fantastic tool but..

- Ligand development for new MOAs timely and costly;
- **10-15K€** per [radiosynthesis-dosing-acquisition-processing]
- Not easy to synchronize with a FTIM usually tunning algorythm downward from MTD which is more cost-efficient
- Coupling factors may be variable (e.g. biological clocks) and be misleading in some rare cases as sleep
- Clozapine would have been overdosed based on historical references

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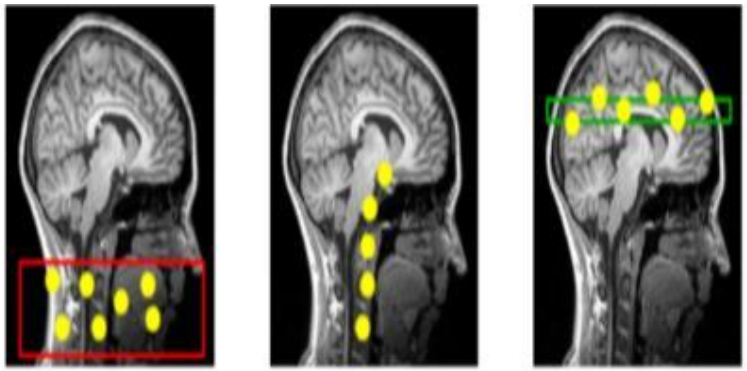
Arterial Spin Labeling

- Magnetisation of blood at the level of carotid arteries by RF (Hanning pulse)
- Signal moves up as tagged blood flows up as a function of CBF
- **Quantitative measure**
- Can operate in resting state or during a task
- Sample size >20



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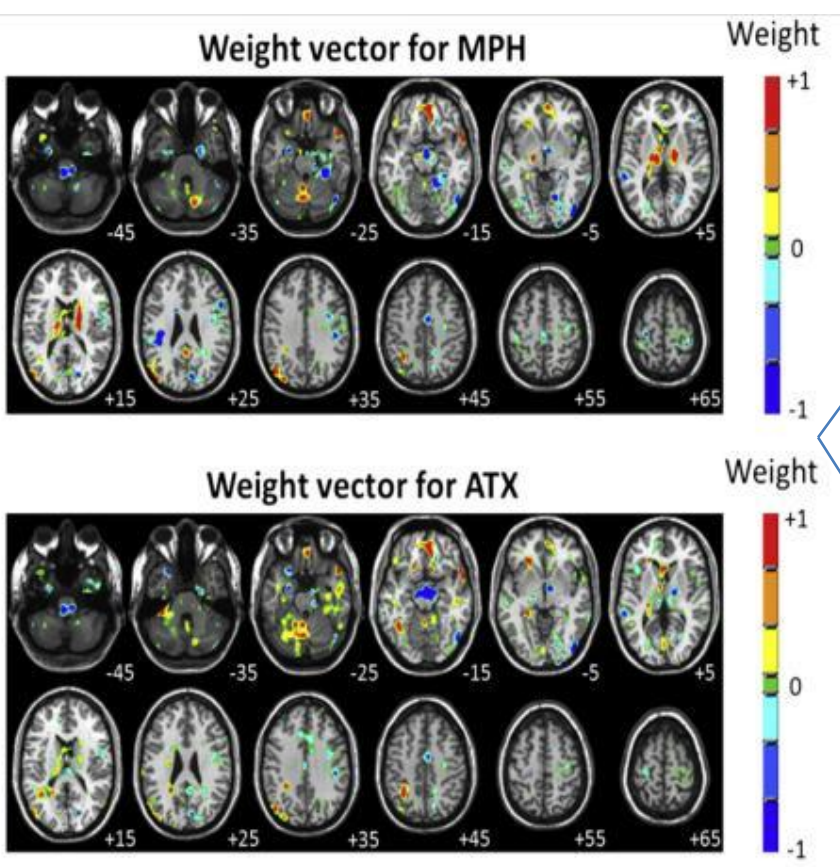
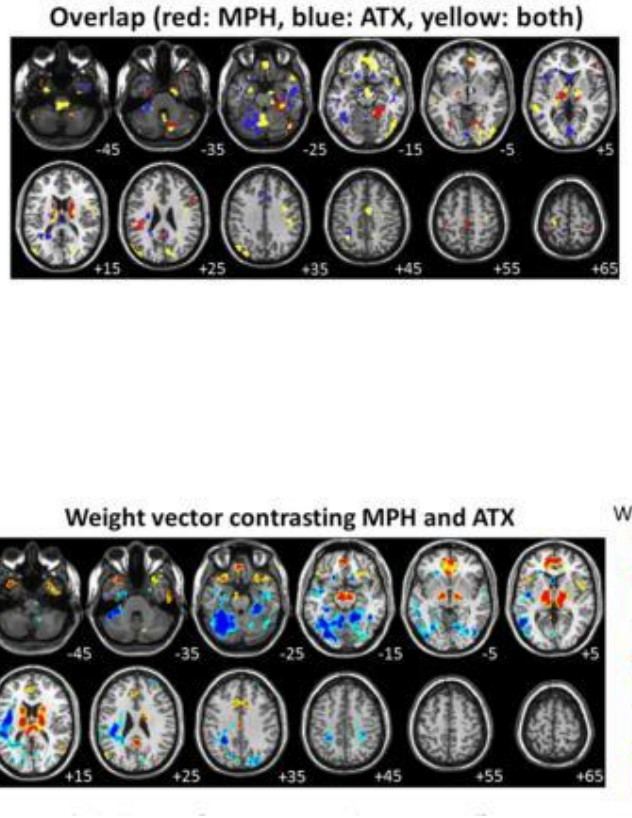
Methylphenidate vs Atomoxetine (& placebo) using ASL





From Marquand et al. Neuroimage 2012

Published data (sensitivity matrix)

- Fentanyl
- Ibuprofen (pre-,post-surgical)
- Methylphenidate vs atomoxetine
- MDMA
- Oxytocin
- Haloperidol vs Aripiprazole
- Dopaminergics in ON-OFF PD patients
- LSD
- Quietapine vs pramipexole
- Methylphenydate in children vs adults

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Next Step

- Who will create a **repository or a database** large enough ? KCl well advanced
- Standardization on its way (A Guideline exists)
- Artificial Intelligence classifiers
- Dose-effect relationships should be considered based on the quantitative nature of the assay

➡ alternative to PET based on a functional response with precision and specificity

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EEG oscillations

- Useful for detecting some functional effects on brain, when a signature exists (silent compounds)
- (Animal telemetry suggested before embarking on a new MOA)
- Low cost and repeatable
- quantitative or not but often based on p-values **Sample depending of the signal magnitude,** requires cross-over or baseline control, in general >16

➡ Inadequate as stopping rule in a 6+2 // group FTIM study

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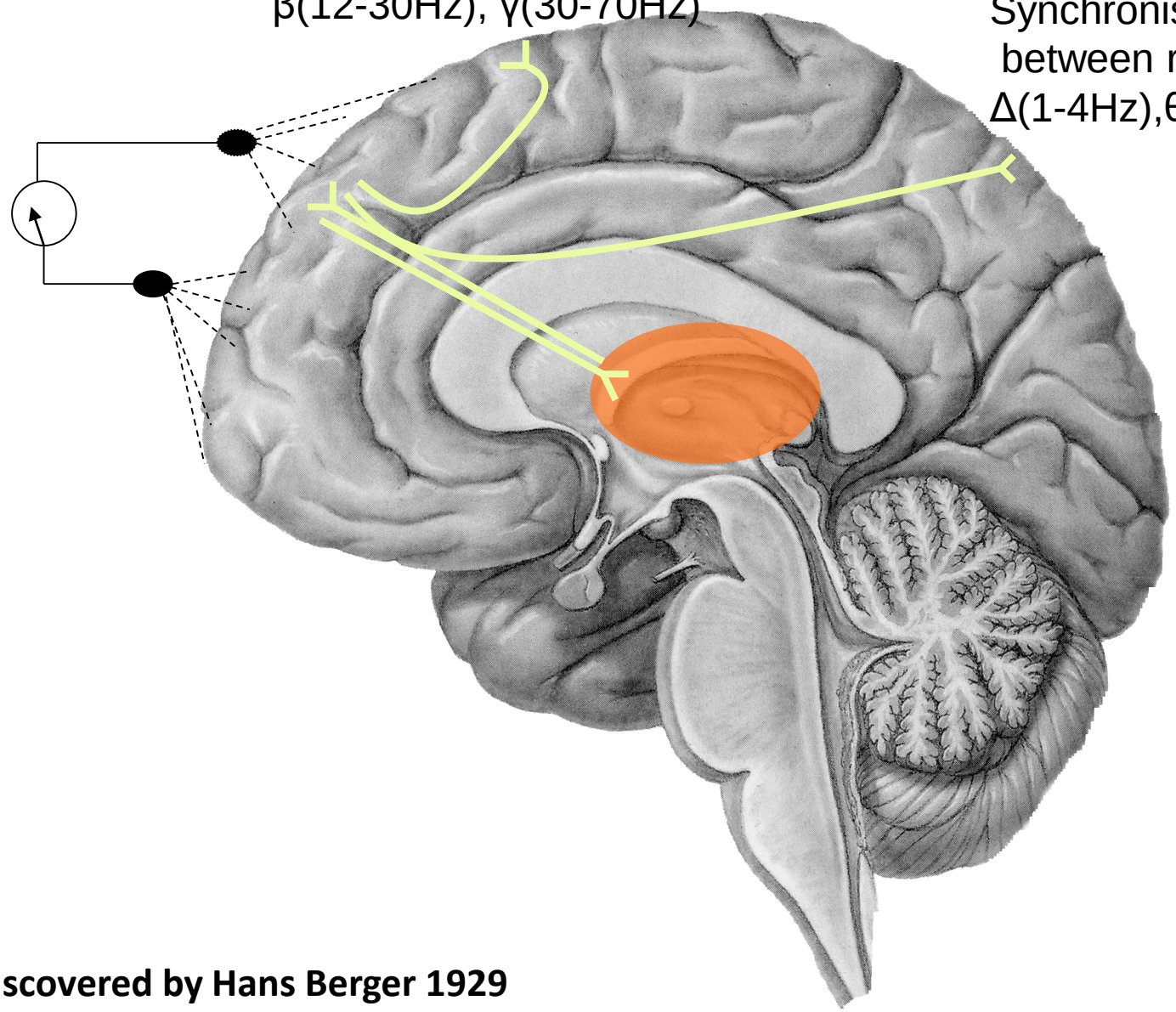
Synchronisation
within a region
β(12-30Hz), γ(30-70Hz)

Synchronisation
between regions
Δ(1-4Hz),θ(4-8Hz),α(8-12)



Discovered by Hans Berger 1929

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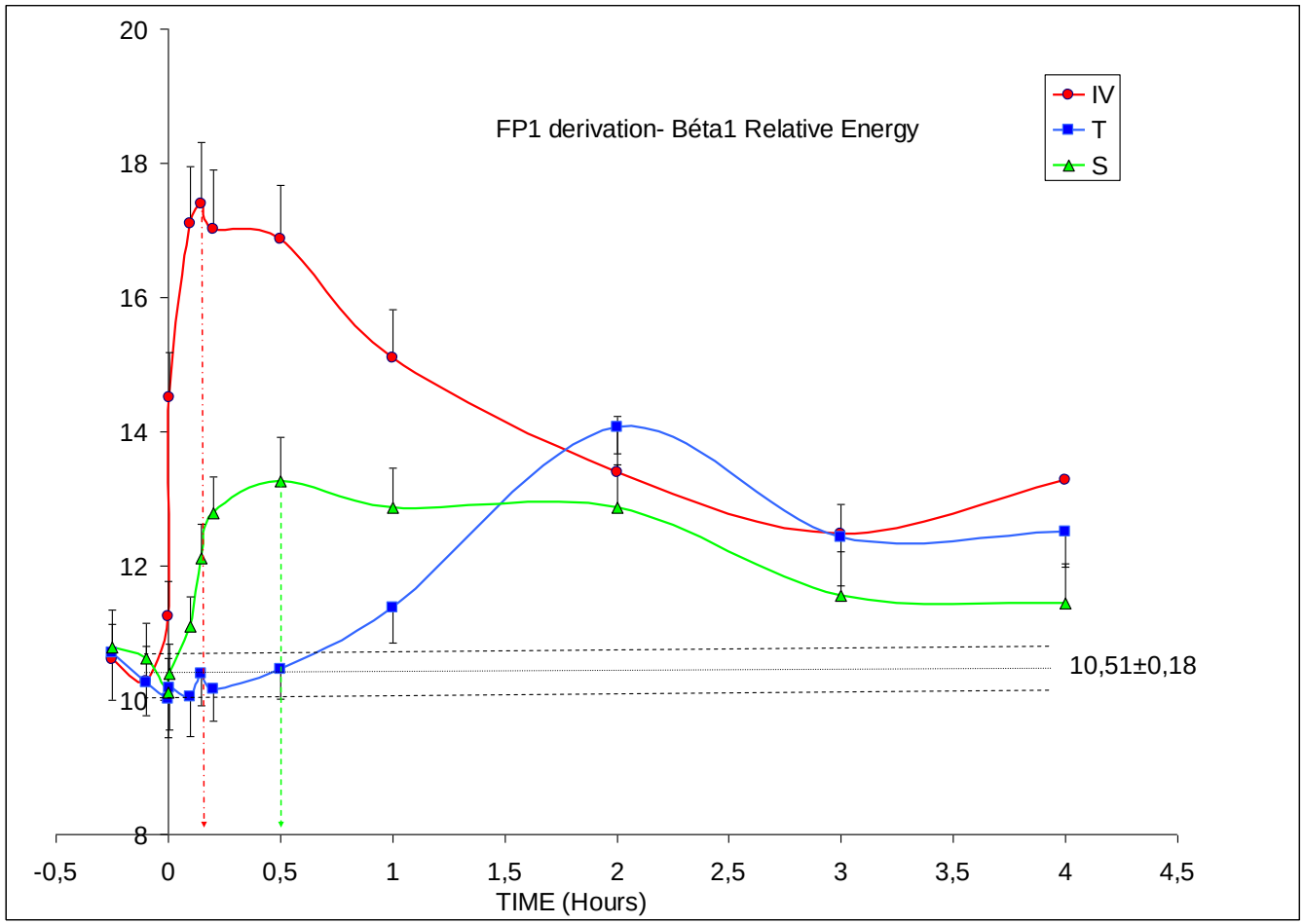
qEEG –Beta1 FP1 : 3 formulations of alprazolam



Daytime qEEG Healthy Humans Sensitivity Matrix

System	Mechanism	δ	Θ	α	β	β	γ
Adenosin	Caffeine	▼	▼	▲	•	•	
Acetyl-choline	M1/M2 antagonist	▲	•	▼	•	•	
	Nicotine	▼	•	▲	▲		
	TC1734(α4β2)	▼	▼	▲	•	▲	
Dopamine	Amphetamine	▼	▼	▲	•	▲	
	Methylphenidate	▼	▼	•	▲	▲	
	D2 blocker	▲	▲	▼	•	•	
Glutamate	MNDA blocker	▼	▲	•	•	•	▲+
GABA	BZD	▲		▼	▲+	▲	
	Zolpidem α1	▲+	•	▼	▲		
	Progesterone	▲		▼	▲	▲	
	Fengabine	•	▲	▼	▲	•	

System	Mechanism	δ	Θ	α	β	β	γ
Norepinephrine	Reuptake blocker	•	▲	▼	•	▲	▲ •
	Beta-blocker			▼			
Serotonin	Reuptake blocker	•	▲	▼	▼	▲	
	$5HT_{2c}$ antagonist	•	•	•	•	•	
	5HT2 agonist (LSD)	▼	▼	▼	▲	▲	
Mixed 5HT+NE	Reuptake blocker	▼	▲	▼	▲	▲	
	SAM Me donor	▼	•	▲	▲	▲	
Tachykinins	NK_3 Talnetant	•	•	▼	•	•	
Opiates	μ	▼	•	▲	•	•	

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Rat Electrocorticogram Sensitivity Matrix (Dark Phase)

System	Mechanism	δ	Θ	α	β	β	γ
Acetyl Choline	Muscarinic blocker (but scopo)	▲	▲	▲	•	▲	
	Scopolamine	▲	•	▲+	•	▲	
	Cholinesterase Inh	▼	•	▼	▼	•	
	Nicotine	•	•	▼	▼		
Dopamine	Agonist/ L-DOPA	▲	•	▼	▼	▼	
	Amphetamine	•	▼	▲	▼	▼	▲
	Methylphenidate	•	•	▲	▼	▼	
	D2 blocker (halo 1mg/Kg)	▲	▲	▲+	▲	▲	
	Apomorphine (0.01 mg/Kg)	▼	•	▲	▲	▲	
	Apomorphine (0.5 mg /Kg)	▲	•	▼	▼	▼	
Excitatory aa	AMPA icv	•	•	•	▲	▲	▲
	NDMA icv	•	•	•	•	•	▲
	MK801/ketamine		▲	•			▲+
	Memantine	•	•	▼	▼	•	•

System	Mechanism	δ	Θ	α	β	β	γ
GABA	Allosteric (BZD)	▲	▲	▼	▲	▲	
	EthOH	▲	▲	▲	•	•	
	Barbiturates	▲	•	▼	▲	▲	
	Alpha-1 zolpidem	▲	•	▼	▲	•	
Norepinephrine	Clonidine α2	•	•	▲	▲	•	
	Desipramine	▼	•	▼	•	▲	▲
	Modafinil (?)	•	•	▼	▼	•	
Opiate	Morphine μ	▲+	▲	▼	•	•	
	Enadoline κ	▲	▲+	•	•	•	
Prostaglandin	COX1-2 inhibitor	•	▲+	•	▲	•	
Serotonin	Reuptake inhibition	•	▲	▼	•	▲	
	$5HT_2$ agonist DOI			▲			

•: lack of consistent effect; ▲: increase ; ▼ : decrease; + high magnitude

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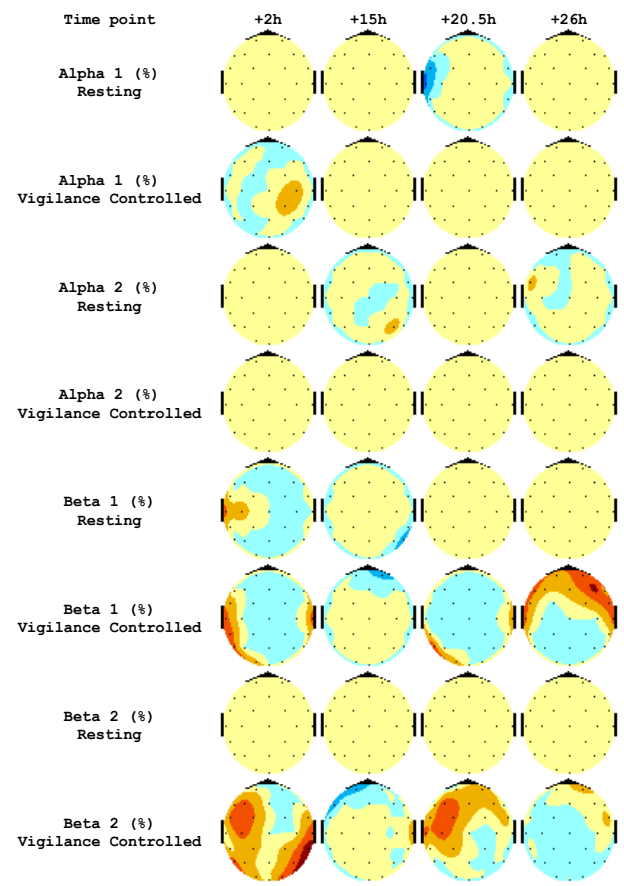
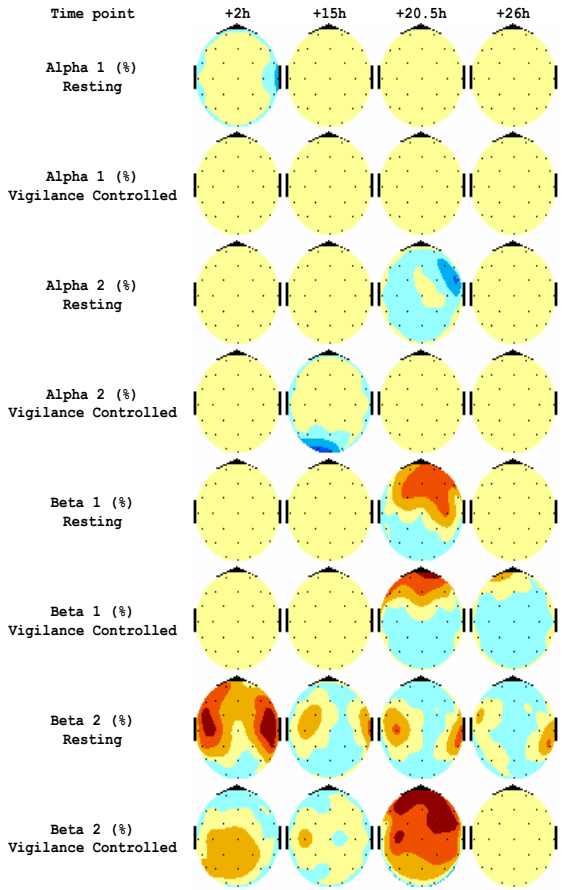
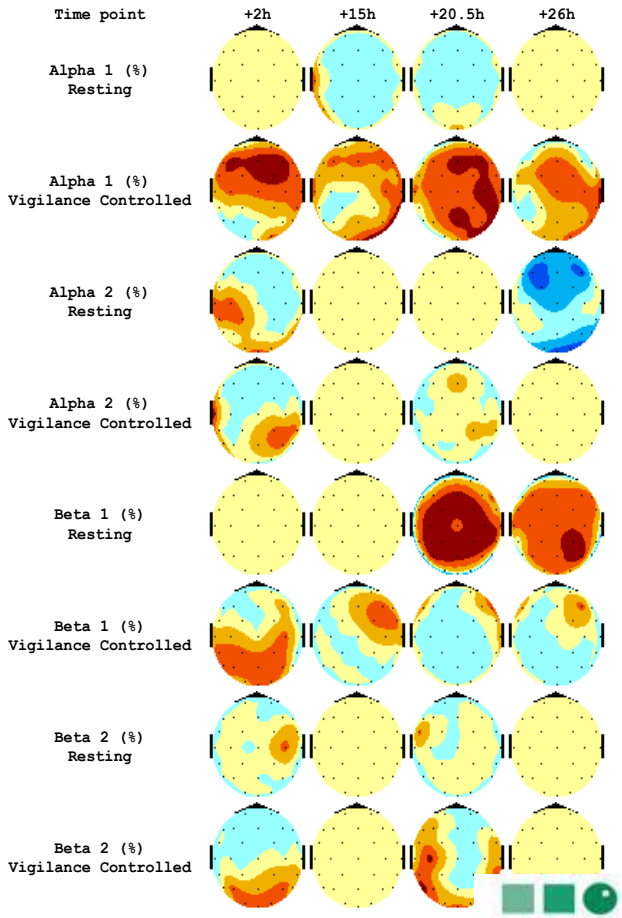
Three dose levels of a modulator of glutamate release



1 mg vs P



3 mg vs P



10 mg

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Other downstream biomarkers

- Sedation using cognitive tasks
  - Adequate design , cross-over
  - Adequate training to the plateau of training effect
  - Less and less compound have this limiting AE (or no more looked at e.g. biologics, oncology etc)
  - With a really careful QC
  - With a carefully defined threshold based on a ROC analysis

➡ With two tests and an adequate sample size some decision-making is possible, if all of the above is met

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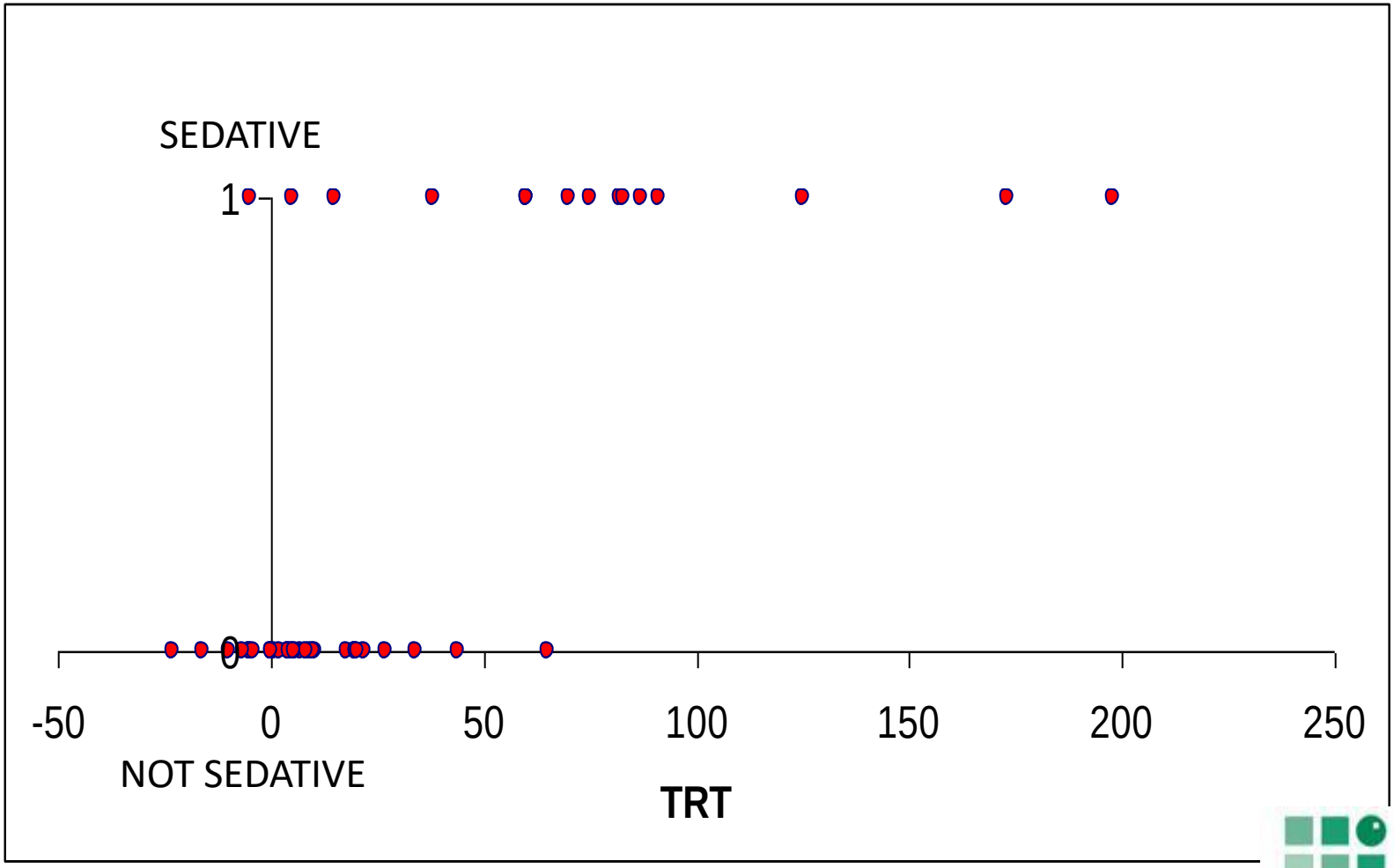
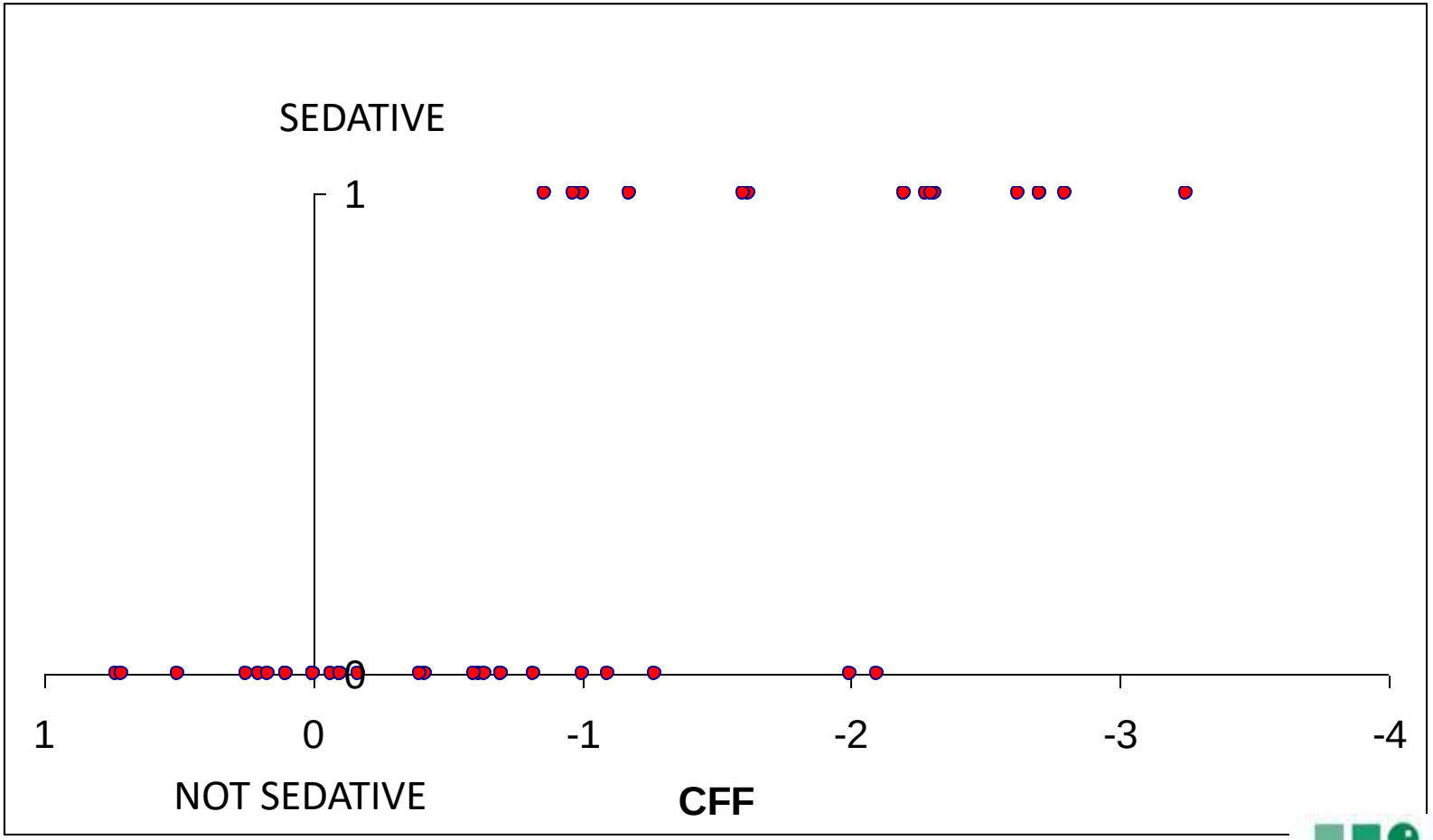
Choice Reaction Time



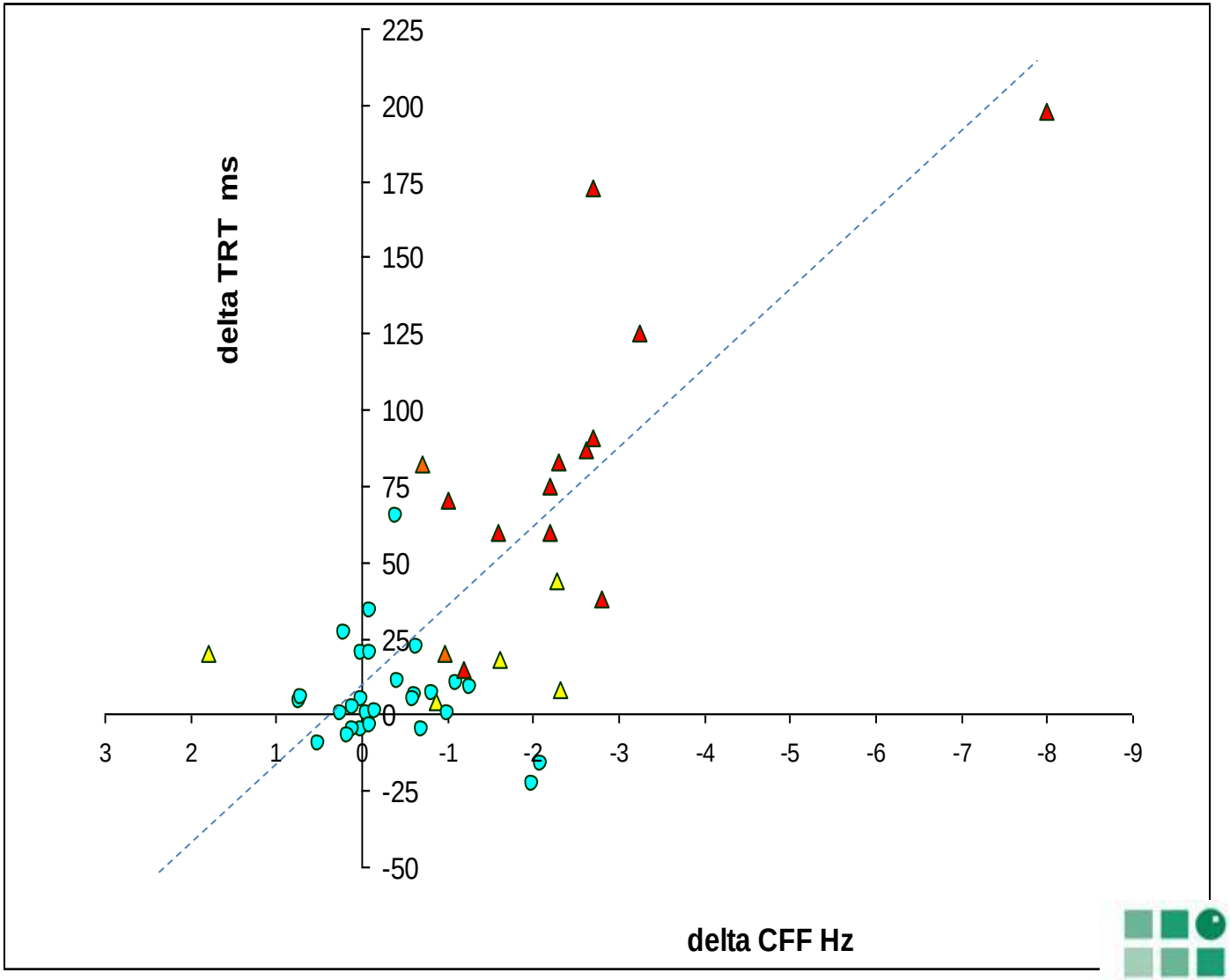
Hindmarch's hardware

Critical Flicker Fusion



Hindmarch's hardware

Combinaison CFF CRT



Pool of 50 studies conducted with Hindmarch's methodology

Conclusions

- A decisionable biomarker (sensitive, specific and calibrated) may be a strategy to limit the exposure in Phase I:
  - During SAD if ran synchroneously to SAD
  - For MAD is a step down PET study is used before it
- Even if ideal exposure for efficacy is reached some overshoot would be needed to handle variability and pharmaceutical development.
- Very few biomakers can have the suitable properties (PET > wet markers-ASL > Pharmacodynamics)
- Costs will be profoundly impacted and a precompetitive strategy would be an option.

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