Precompetitive Consortium for the use of EEG as a CNS Translational Biomarker

P.Danjou MD PhD

Phase I Club , Nice, 11 April 2013

BIOTRIAL

Hurdles in CNS Drug Development

- **Longest duration of development** over all Therapeutic Areas[1]
  - CNS: 8,1 years Phase I-III; 1,9 years for Registration, **Total =10**
  - Oncology: 6,1 years Phase I-III; 0,7 years for Registration, **Total =6,8**
- **Overall success rate** low 8.2% (anti-infective 23,9%)
- **Phase III failure more frequent 54%**: aprepitant in depression; Dimebon® in Alzheimer's disease, SANOFI's amibegron in depression etc
- **Lack of incentive of a high price** , still chronic /recurring pathologies

1:DiMasi et al. Clinical Pharmacology & Therapeutics 2010

Hurdles in CNS Drug Development

- **Longest duration of development** over all Therapeutic Areas[1]
  - CNS: 8,1 years Phase I-III; 1,9 years for Registration, **Total =10**
  - Oncology: 6,1 years Phase I-III; 0,7 years for Registration, **Total =6,8**
- **Overall success rate** low 8.2% (anti-infective 23,9%)
- **Phase II failure more frequent 54%**: aprepitant in depression; Dimebon® in Alzheimer's disease , SANOFI'a amibegron in depression etc
- **Lack of incentive of a high price** , still chronicity/recurrence

- Price of CNS R_X less than in Oncology (1log) and much less than for Orphan drugs (2-3 logs) . For a year of R_X:
  - Aripiprazole **1356€**/an; s-citalopram **348**€/an
  - Non small cell lung carcinoma **13,969** €/an [INSERM 2010]
  - Soliris® -Hemolytic-Uremic syndrome, Alexion : **409,000**$/an
  - Cerezyme®, Gaucher's disease, Genzyme : **209,000**$/an

1:DiMasi et al. Clinical Pharmacology & Therapeutics 2010

Resulting effects on Motivation

- **Negative effects** : Some Companies announced a termination of CNS programs e.g. Astra-Zeneca, Some closed some Neuroscience Units e.g Merck Sharp & Dohme or downsized R&D in this domain (Pfizer-Wyeth)

- **Positive effects** : More pro-active(versus observational) search of suitable Biomarkers for earlier termination and more efficient selection of drug candidates is ongoing with several constraints:

  — Proof or Mechanism Biomarker :
  *Involving target organ (Brain)
  *Involving a response and not only Receptor Occupancy
  — Translatable between species
  — Sensitive
  — Reliable over test-retest
  — Suitable for PK/PD and multiple measurements
  — Widely available preclinically and clinically
  — Controlled cost

Potential Current Utility of EEG as a CNS Biomarker in Drug Development

At present **resting qEEG has several advantages** as a biomarker platform for putative centrally active compounds, since:

- recording and analysis techniques are relatively **low cost and broadly available** preclinically as well as clinically
- qEEG has a number of characteristics of an "ideal" biomarker, as it is continuous, objective, repeatable, reproducible, translatable and sensitive
- qEEG can be easily included in early studies as a biomarker to confirm target **engagement and activation**
- it provides **PD outcomes for PK-PD modelling** and thereby a fuller understanding of the pharmacology earlier in the programme ("window into the brain")

Additional value

- qEEG has even face- and construct- validity for the effects of drugs in several target indications (insomnia, epilepsy)
- there is increasing evidence for the use of qEEG as :
  - a prognostic biomarker for the cognitive deficits in MCI and Alzheimer,
  - a drug-response biomarker in major depressive disorder
  - a marker of genetic risk for ADHD

BIOTRIAL

The fall and rise of EEG as a CNS biomarker

- **Despite being a longstanding and well-established technology, EEG has been devalued by the industry largely due to:**
  - Disbelief in the value of EEG as a biomarker due to past failures with a wide variety of causes, including **'over-promising'** what it can deliver
  - The advance of imaging techniques, which were thought to supersede EEG as a "window into the brain", whereas current knowledge pleads for **both techniques to be regarded as complementary.**
  - **Lack of standardisation** in EEG recordings and study designs, leading to:
    - Problems with data sharing / pooling
    - Problems when trying to compare proprietary EEG data with data from literature
    - Costly attempts by most major Pharma to set up their own (pre)clinical reference EEG databases
  - Incomplete knowledge of the translatability of pharmaco-EEG effects from animal to man
- **However, there is a recent revival of the use of EEG as a CNS biomarker in drug development due to improved capabilities due to technical advances**:
  - Improved EEG **recording equipment** enables easier incorporation into clinical studies, increased bandwidth, and better artefact and noise reduction
  - Greater data **storage capabilities** enable all data to be stored and analysed
  - Improved data analysis techniques enable the study of novel measures such as coherence and cordance and source localisation

BIOTRIAL

A State of the Art Significant Sampling

Translational CNS Summit | Boston | 21st – 23rd May 2013

Keynote Session Panel Session Networking Session

Day 1 Continued — 22nd May 2013

Optimizing the Use of Imaging Within your Clinical Development

4.00 **Inserting Imaging in CNS Drug Development: Driver for Success or a Waste of Time?**

- CNS drug development is difficult – how can imaging make life easier?
- Inserting imaging across clinical drug development to effectively visualize brain function
- Objectifying data: from symptoms to disease modification

David Borsook, Director, P.A.I.N. Group, Boston Children's Hospital

4.30 **Case Study: Bridge through Darkness - Translational Studies Supporting AZD6765 - A Low-Trapping NMDA Channel Blocker for Treatment of Refractory Depression**

- Learning from biomarker studies using qEEG and fMRI
- Phase II data demonstrates significant therapeutic benefit in patients
- Cortical disinhibition likely drives the therapeutic action of low-trapping NMDA channel blockers
- How imaging helped to inform these conclusions

Michael Quirk, Director, AstraZeneca

5.00 **Case Study: The Preclinical Development of a PDE10 PET Tracer**

- Validating new tracers for human disease
- Navigating interspecies differences when handling novel tracers
- How to extrapolate your findings to predict performance in man

Bob Fremeau, Scientific Director, Amgen

5.30 **Multimodal Magnetic Resonance Imaging: A Key Translational Medicine Strategy**

- Using MRI to predict success early in clinical development
- How you can use imaging to select patients likely to respond to therapy
- Improving the current use of imaging in drug development

Juan Chavez, Experimental Medicine, Neuroscience, Biogen Idec

6.00 **Chair's Closing Remarks**

BIOTRIAL

Comparison of Functional CNS Biomarker Techniques

	RO-PET	FDG-PET	fMRI	MEG	qEEG
Measure of target engagement?	Yes	By inference	By inference	By inference	**By inference**
Measure of pharmacological action / expression?	No	Yes	Yes Paradigm	Yes	**Yes**
Direct measure of neuronal function?	N/A	No *(metabolism)*	No *(blood flow / oxygenation)*	Yes *(magnetic field)*	**Yes** *(electric field)*
Temporal resolution	Low (5logs)	Low	Medium (4logs)	High	**High**
Spatial resolution	High	High	High	High	**Low**
Can be integrated with SD/MD studies?	No	No	Potentially, if available at Phase 1 site	Potentially, if available at Phase 1 site	**Possible in many cases**
Availability	Medium	Medium	Medium	Very low	**High**
Cost	$$$ - $$$$	$$$	$$$	$$	**$**

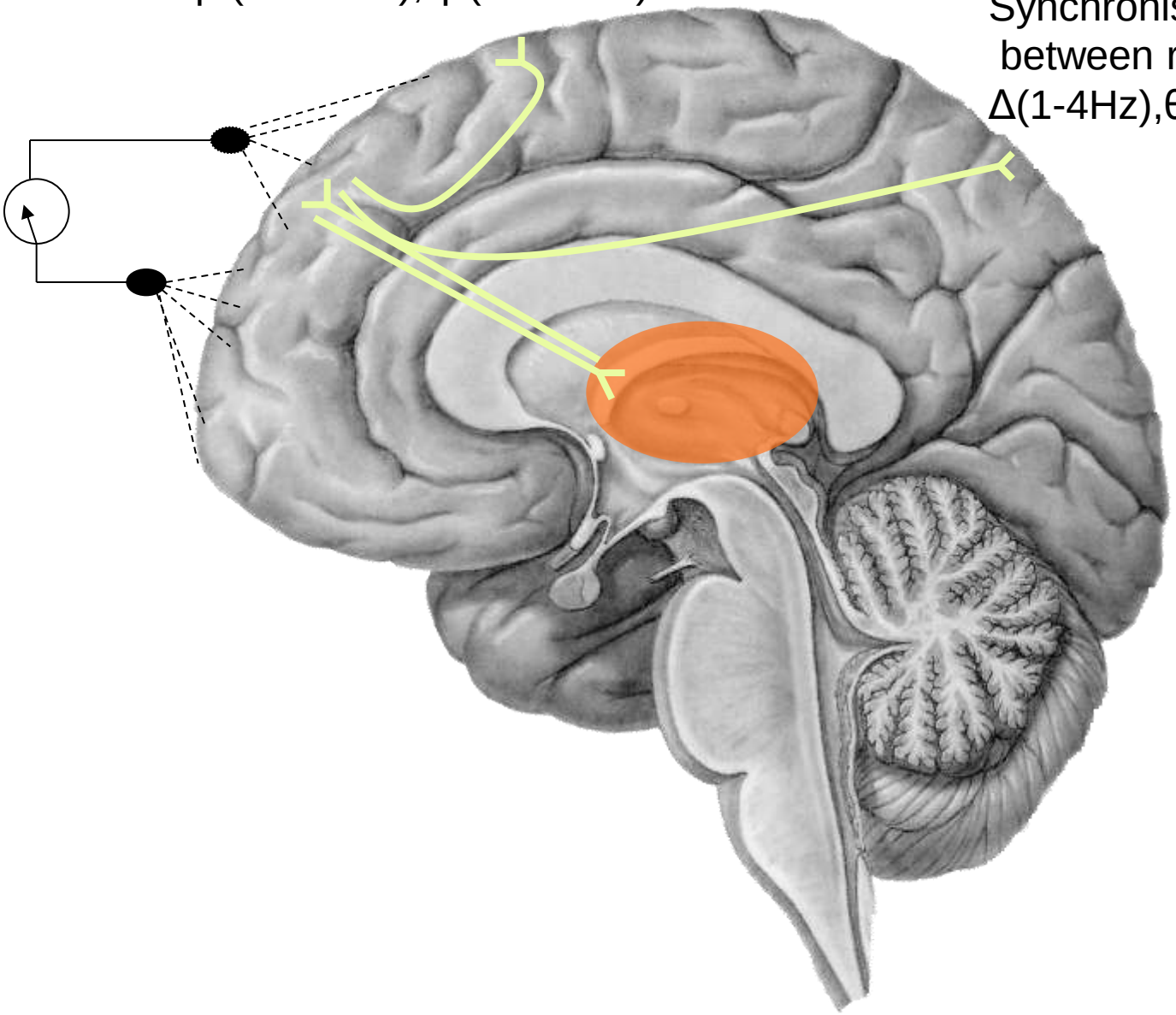
BIOTRIAL

EEG: Surface Recording

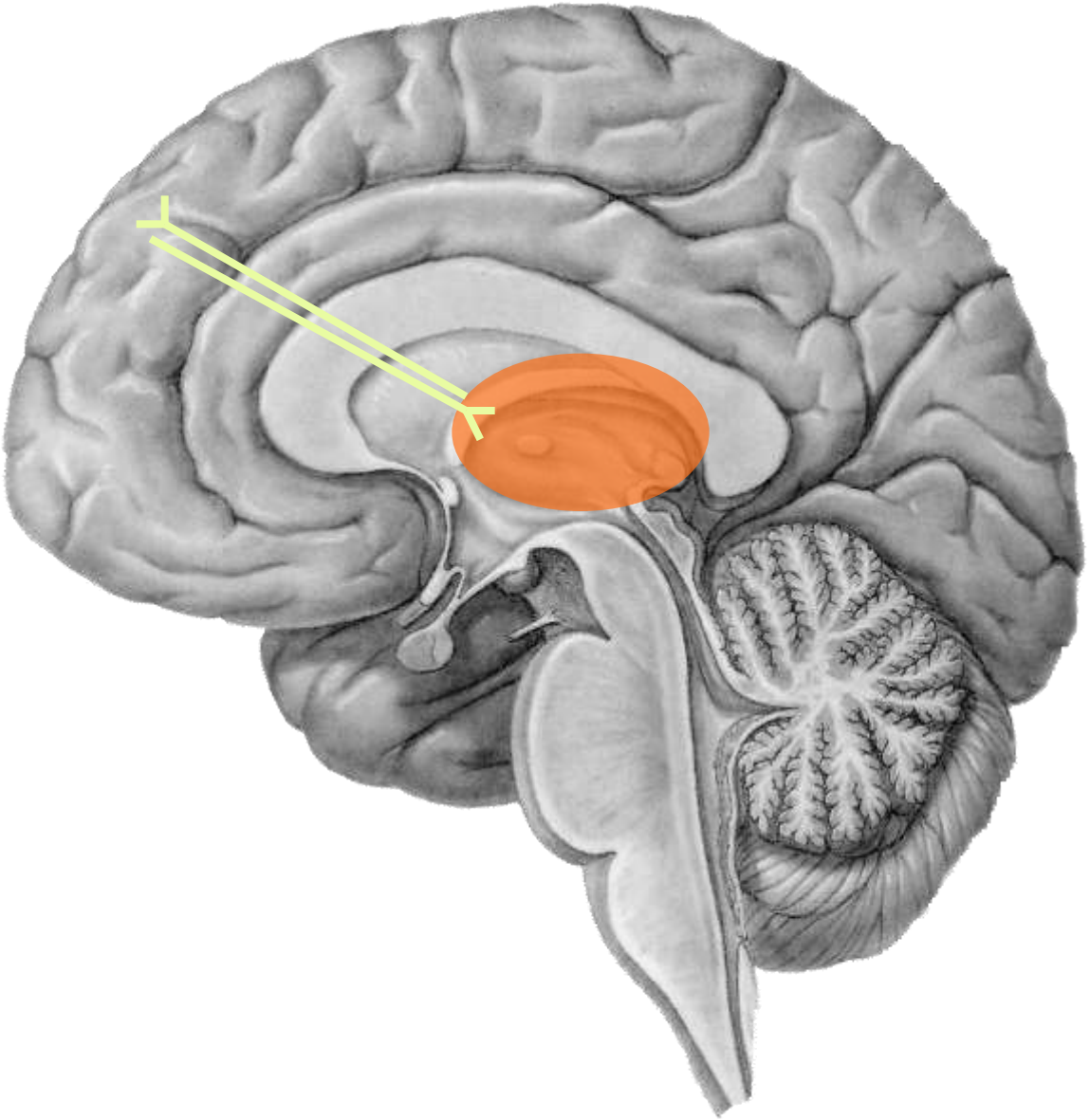
BIOTRIAL

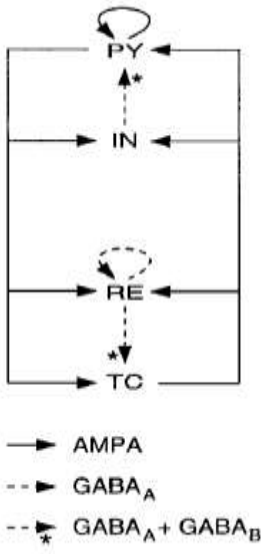
Synchronisation
within a region
β (12-30Hz), γ (30-70Hz)

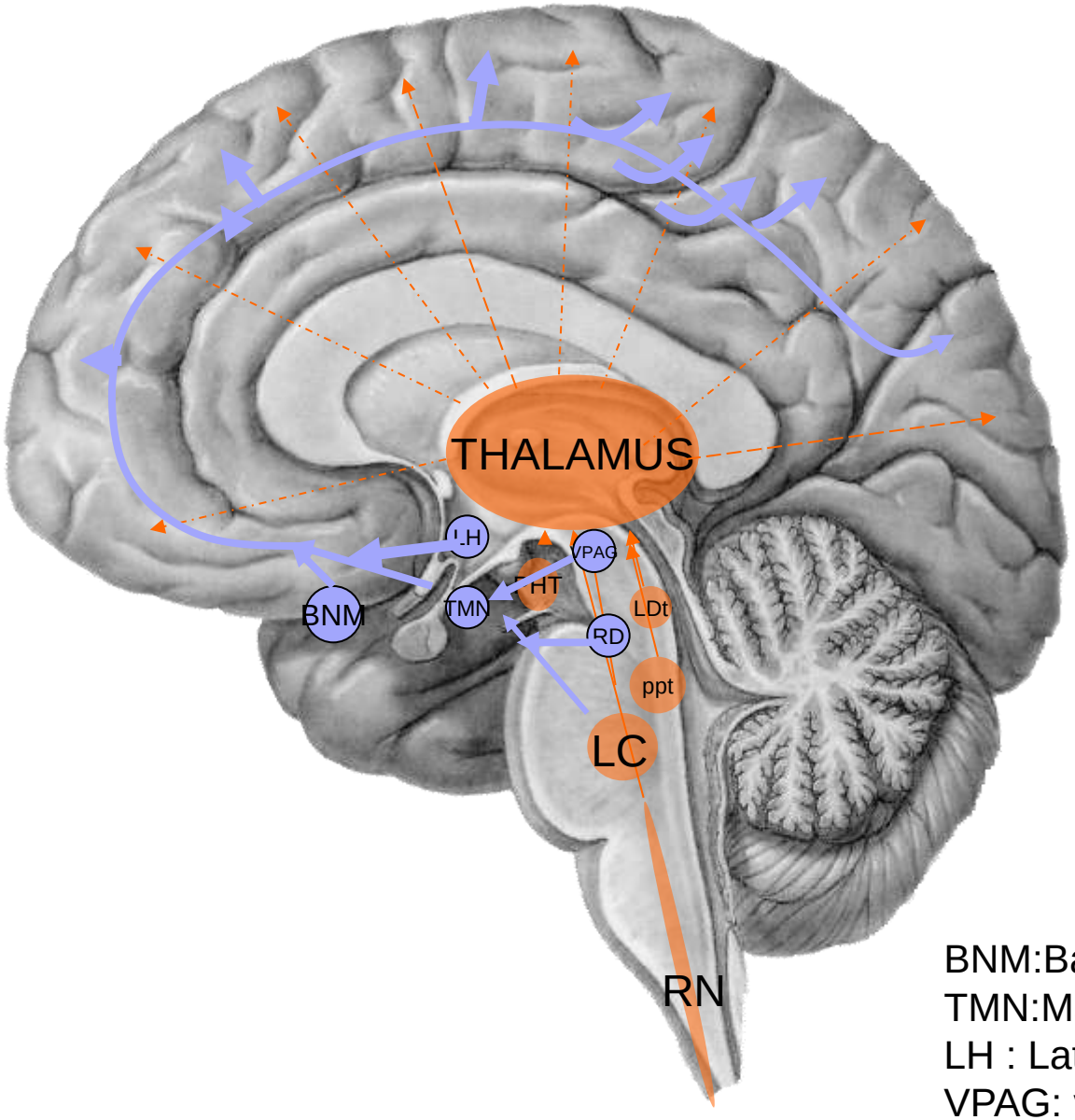
Synchronisation
between regions
Δ(1-4Hz),θ(4-8Hz),α(8-12)



Corticothalamic loops

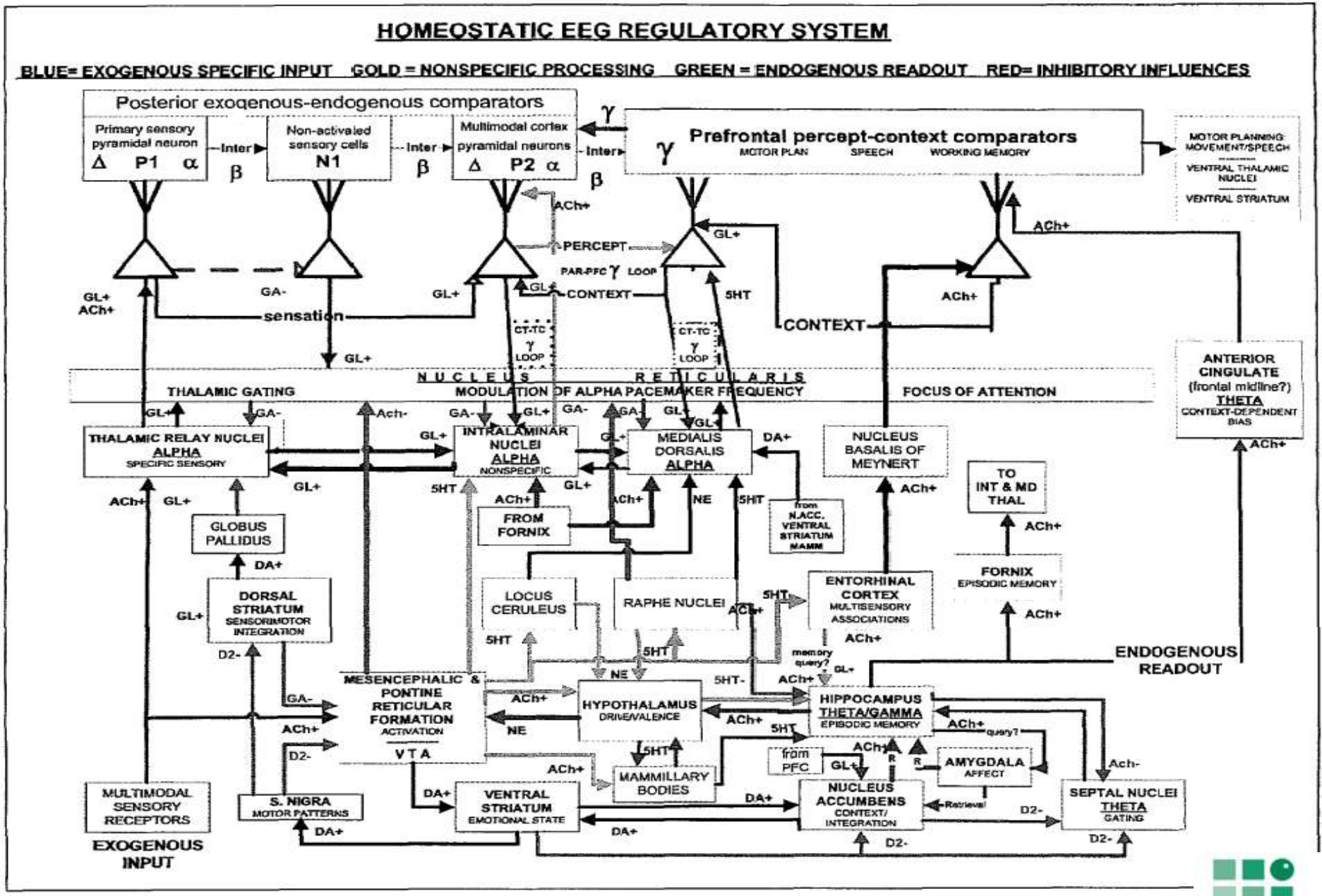






BNM:Basalis Nucleus Meynert
TMN:Mammilary Tubercle
LH : Lateral hypothalamus
VPAG: ventrea periacqueducal Grey matter
RD:Raphe Dorsalis

BIOTRIAL



John Roy's functional scheme

BIOTRIAL

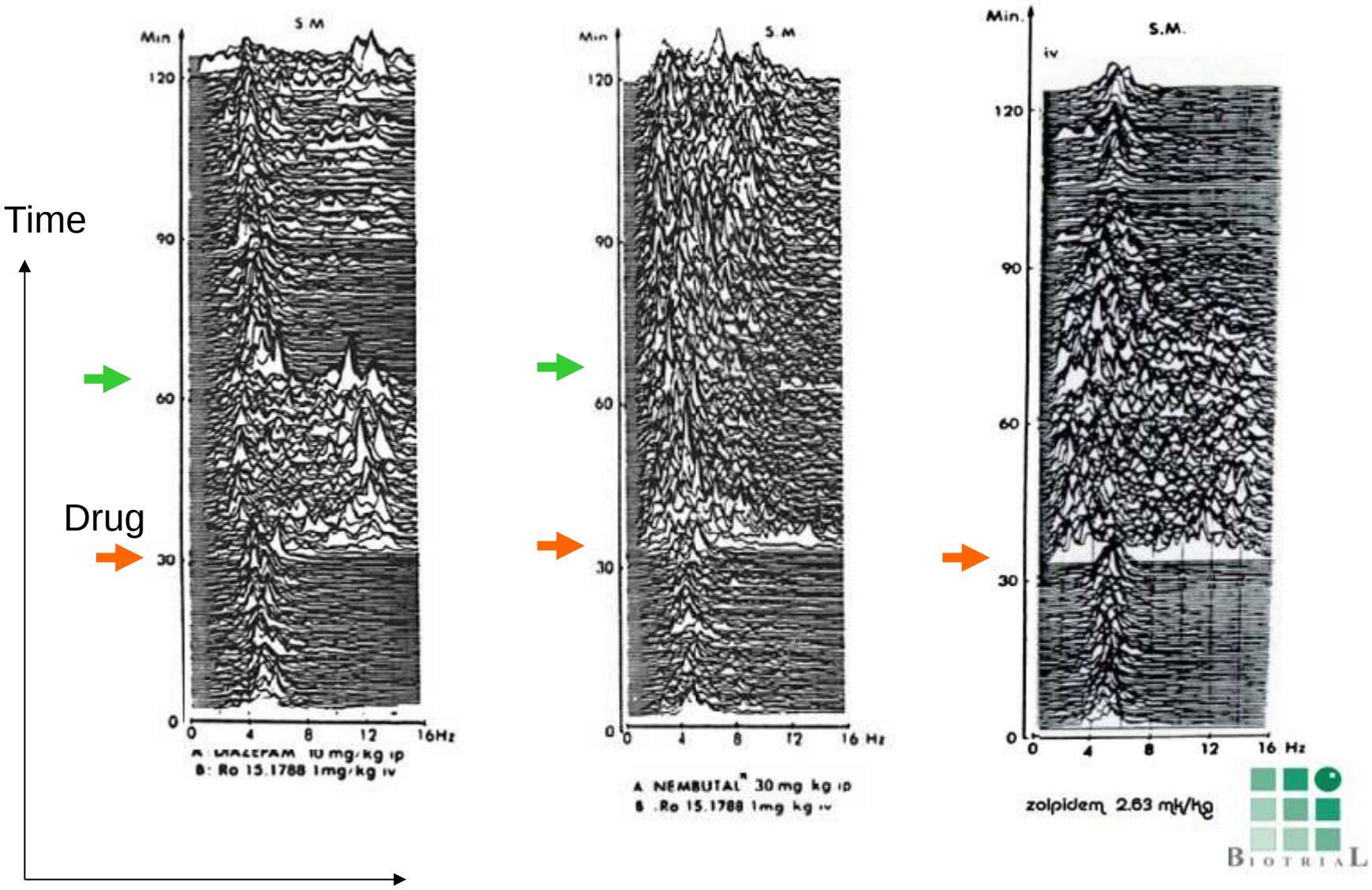
Rat Electrocorticogram Sensitivity Matrix (Dark Phase)

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

Rat Electrocorticogram



Depoortere 1985,Garrigou-Gadenne et al. 1988

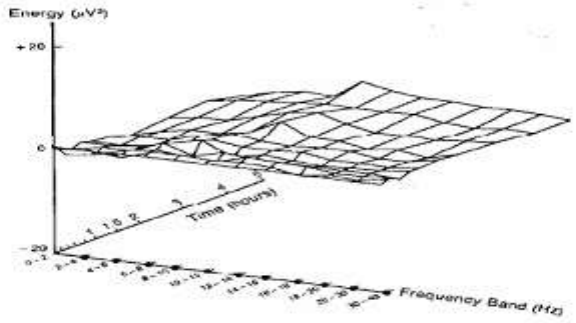
Daytime qEEG Healthy Humans Sensitivity Matrix

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

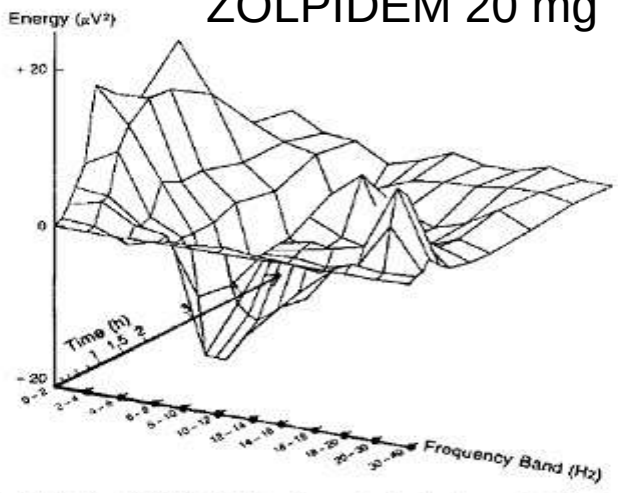
System	Mechanism	δ	Θ	α	β	β	γ
Norepinephrine	Reuptake blocker	•	▲	▼	•	▲	▲
	Beta-blocker			▼			
Serotonin	Reuptake blocker	•	▲	▼	▼	▲	
	$5HT_{2c}$ antagonist	•	•	•	•	•	
	5HT2 agonist (LSD)	▼	▼	▼	▲	▲	
Mixed 5HT+NE	Reuptake blocker	▼	▲	▼	▲	▲	
	SAM Me donor	▼	•	▲	▲	▲	
Tachykinins	NK_3 Talnetant	•	•	▼	•	•	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

Human qEEG time-frequency

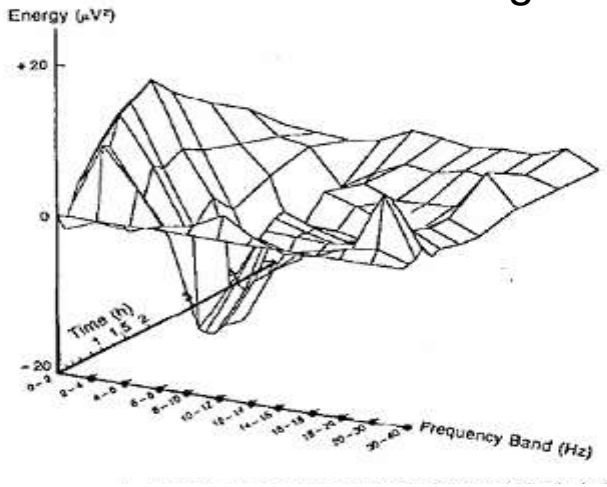
PLACEBO



ZOLPIDEM 20 mg

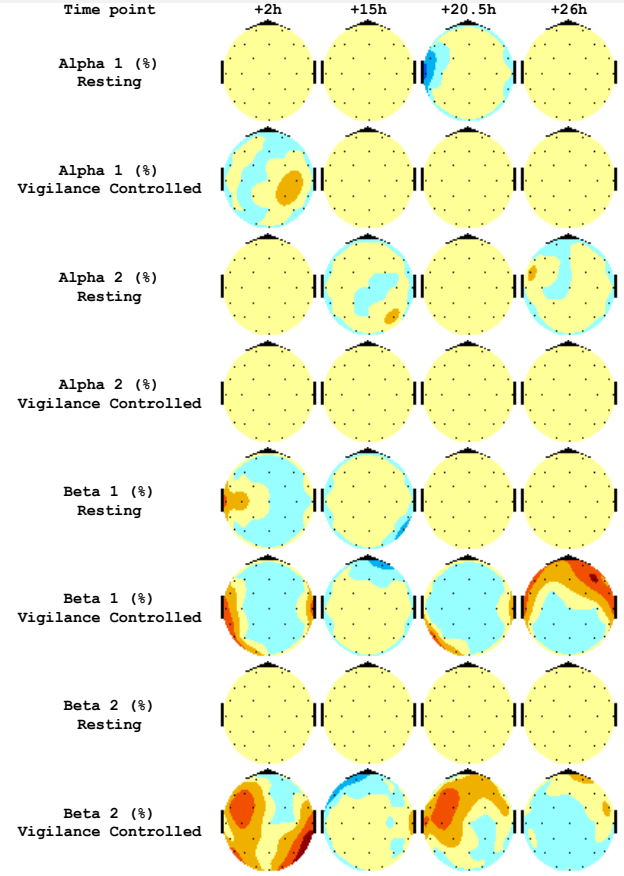


ZOLPIDEM 5 mg

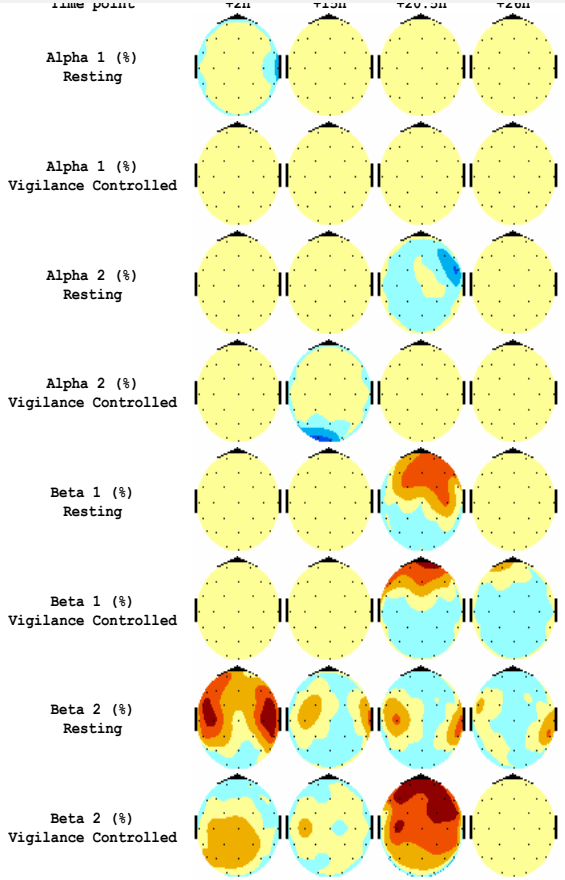


Danjou et al. 1992 personal communication/ published Patat et al. 1994

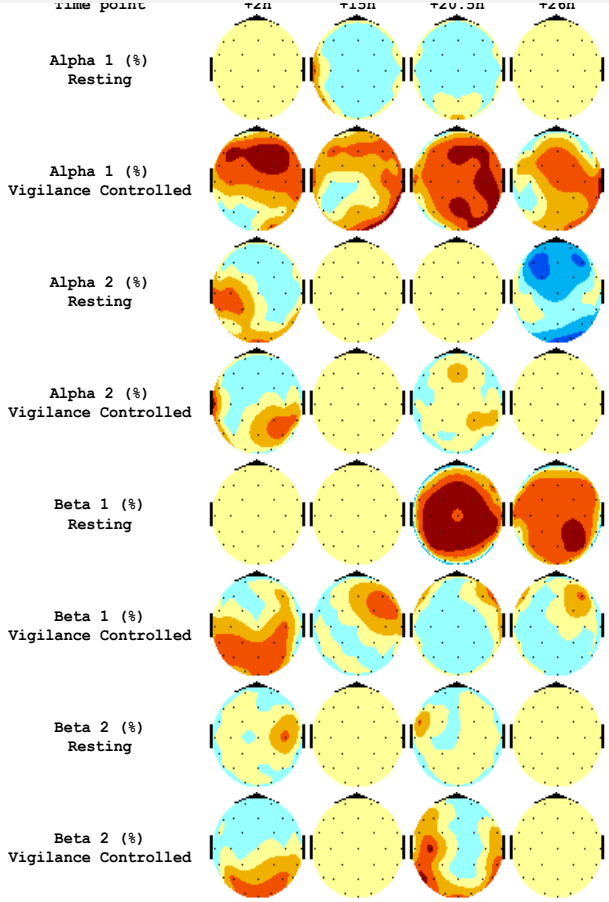
Three dose levels of an alerting compound



1 mg vs P



3 mg vs P



10 mg vs P

International Pre-competitive Pharmaco-EEG Consortium (IPPEC)

Motivation, Objectives and Proposal for a Project to Develop Electroencephalography (EEG) as a CNS Biomarker in Drug Development

Objectives of the Proposed Project

- To establish industry-wide standardisation of pharmaco-EEG recording techniques
- To set-up a global Centralised Data Repository (CDR) to store shared EEG data and enable access by the consortium members and other partners
- To populate the CDR with a comprehensive set of placebo and reference wake EEG data in healthy volunteers
  - Acute administration of a comprehensive range of drug classes will be covered by this project

Benefits to Consortium Members

- Consortium members will have full access to the CDR, containing a rich dataset of clinical EEG recordings covering a wide range of drug classes administered acutely to healthy volunteers, which
  - is impossible for a partner to achieve individually at a reasonable cost;
  - provides clinical data for comparison with that from in-house animal models;
  - provides normative data for future clinical studies (to be used as reference data for comparison with positive control results or to allow a positive control arm to be omitted)

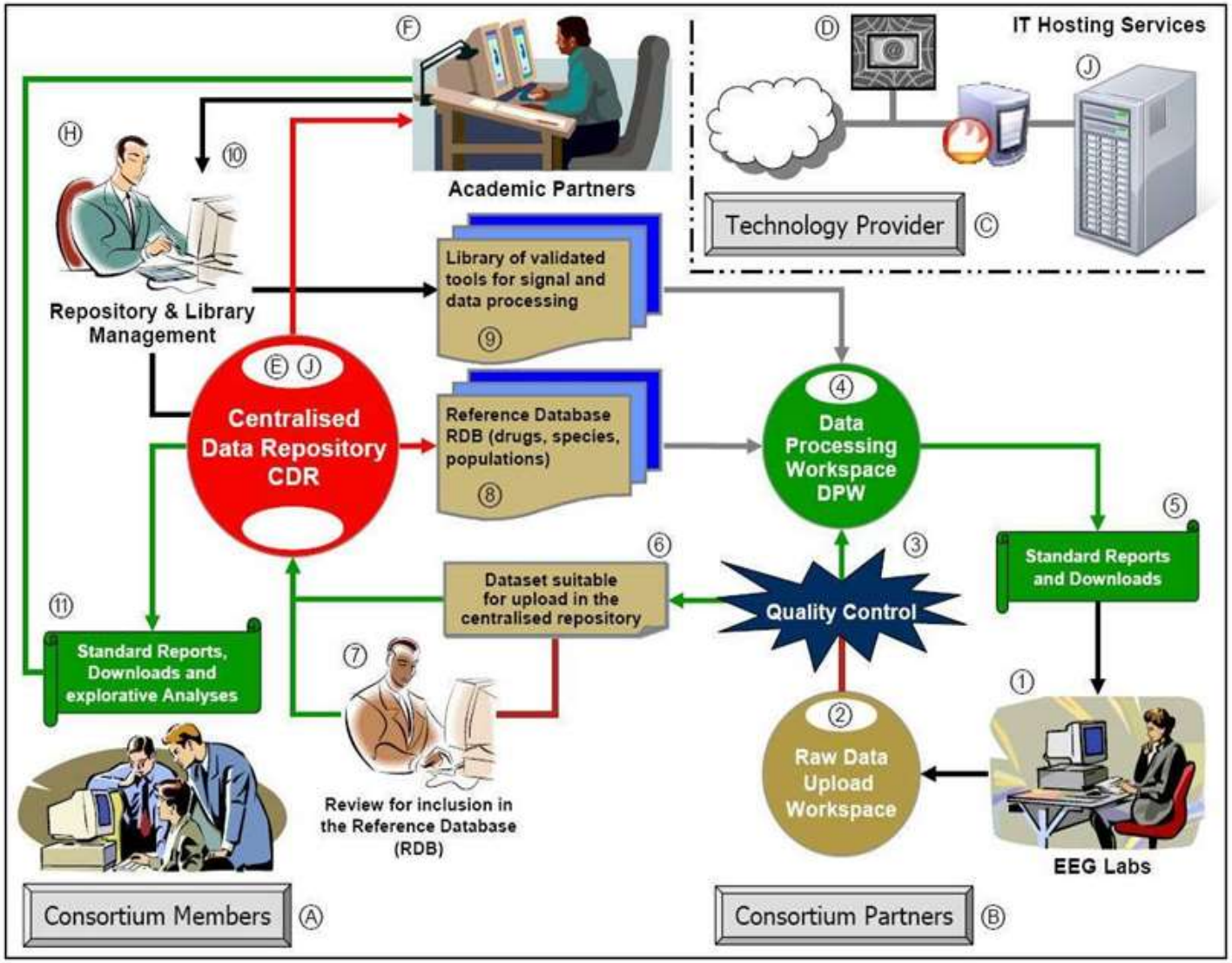
- The CDR could be used as the backbone of future projects to
  - assess inter-species translatability for a wide-range of drug classes;
  - develop novel signal- and data-processing techniques to enhance the utility of EEG to the pharmaceutical industry
  - increase the scope of the datasets (e.g. to cover chronic administration)

- Per its initial design, the informatics platform of the CDR will also support the future storage and processing of PSG and ERP signals without additional development costs

EEG Pre-competitive Initiative – History and Objectives

- The Consortium emerged during the second half of 2010 to establish standardised EEG recording and analysis techniques in conjunction with a global centralised data repository of placebo and reference EEG data.
- Overall objectives
  - Promote the use of EEG as a translational biomarker for the development of CNS-active compounds by sharing standards and relevant data
  - Accelerate the drug development process by enabling comparative analyses from different studies using various reference drugs, species, conditions and study populations (healthy volunteers and patients) based on both clinical and pre-clinical EEG data
  - Focus initially on quantitative wake EEG, with the possibility to include PSG and ERP at a later stage
- The Consortium initiative is actively supported by a number of large pharmaceutical companies
  - Abbott, Astra Zeneca, Johnson & Johnson, Lundbeck, Pfizer, Servier, and UCB Pharma
  - Others have expressed interest: Roche, Eli Lilly, BMS, Merck, Novartis, Orion, Eisai

Bioinformatics – Structure of the Centralised Data Repository



Reference Datasets – Selected Active Compounds

Part A

- Lorazepam (2.0 mg)
- Nicotine (1.0 mg nasal spray)

Part B

- clozapine
- donepezil
- ketamine
- memantine
- scopolamine
- methylphenidate
- s-citalopram
- haloperidol
- zolpidem
- modafinil
- amphetamine
- risperidone

Compounds were selected using a voting procedure involving all currently active Consortium participants

Status

Preparation:

- Process ongoing since 2010 handled by Forenap then IPEG then IPPEC
- Two guidelines published (EEG and PSG in Humans) for **standardization**
- Animal Guidelines on their way
- Two steps of funding (first completed: Abbott, Astra-Zeneca, Biotrial, Johnson & Johnson, Pfizer, Servier, UCB Pharma)
- Legal Entity about to be created with members willing to go to step 2 by 3Q-4Q2013
- Oséo support seeked in France

Production:

- Data wharehouse building starting first
- Lag time for populating the CDR with **selected positive controls**
- New Algorythms development and starting at the same time as database population
- Later steps animal data acquisition after animal EEG guideline is issued
- Sleep data acquisition as a second wave.

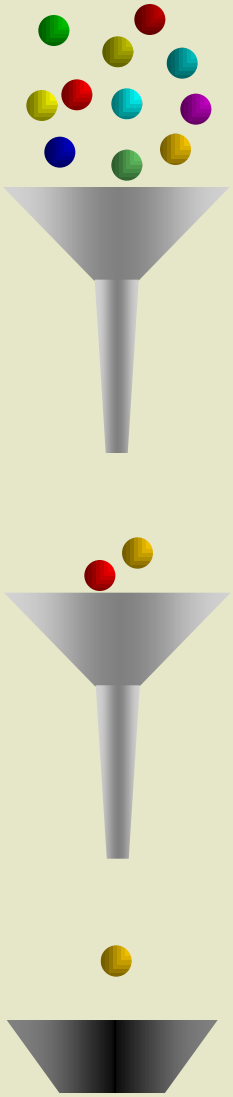
Backup slides

Conventional program

Proof of Concept
10 projects enter
Cost=$200m

PIIb/PIII/Reg
2 projects enter
Cost=$400m

Market
1 project succeeds
Total cost=$600m



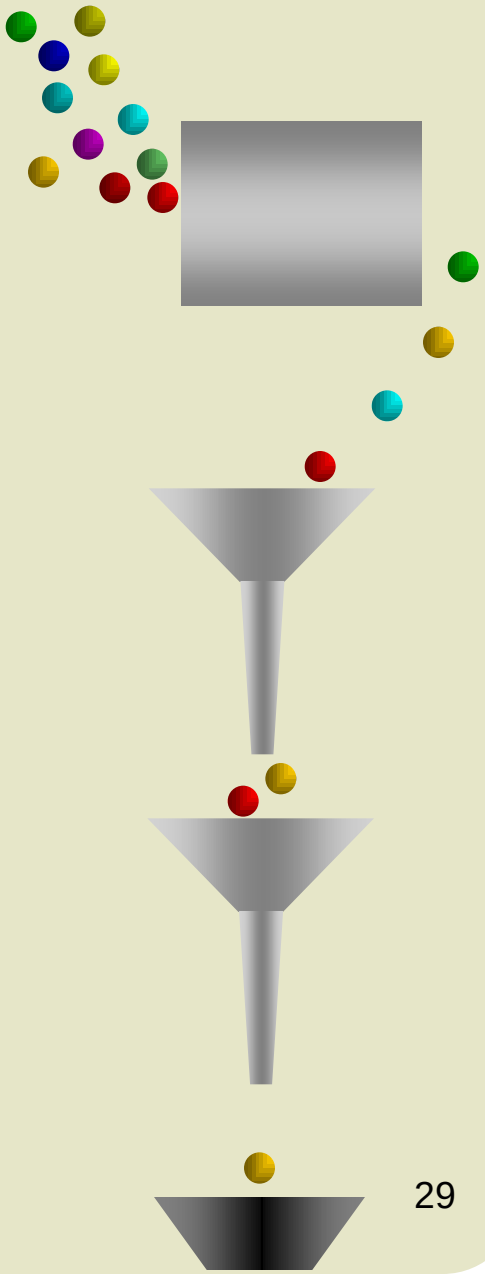
Biomarker program

Biomarker study
10 projects enter
Cost=$20m

Proof of Concept
4 projects enter
Cost=$80m

PIIb/PIII/Reg
2 projects enter
Cost=$400m

Market
1 project succeeds
Total cost=$500m



Adapted with permission from Wise & Preston, Drug Discovery Today, 2010. *Financial figures for illustration only.*

Phase Transitions

Table 3 Phase transition and clinical approval probabilities by therapeutic class for self-originated compounds first tested in humans from 1993 to 2004

Therapeutic class	Phase I–II (%)	Phase II–III (%)	Phase III–RR (%)	RR–approval (%)	Clinical approval success rate (%)
Antineoplastic/immunologic	71.8	49.0	55.3	100	19.4
Cardiovascular	62.9	32.4	64.3	66.7	8.7
CNS	59.6	33.0	46.4	90.0	8.2
GI/metabolism	67.5	34.9	50.0	80.0	9.4
Musculoskeletal	72.4	35.2	80.0	100	20.4
Respiratory	72.5	20.0	85.7	80.0	9.9
Systemic anti-infective	58.2	52.2	78.6	100	23.9
Miscellaneous	62.8	48.7	69.8	91.3	19.5

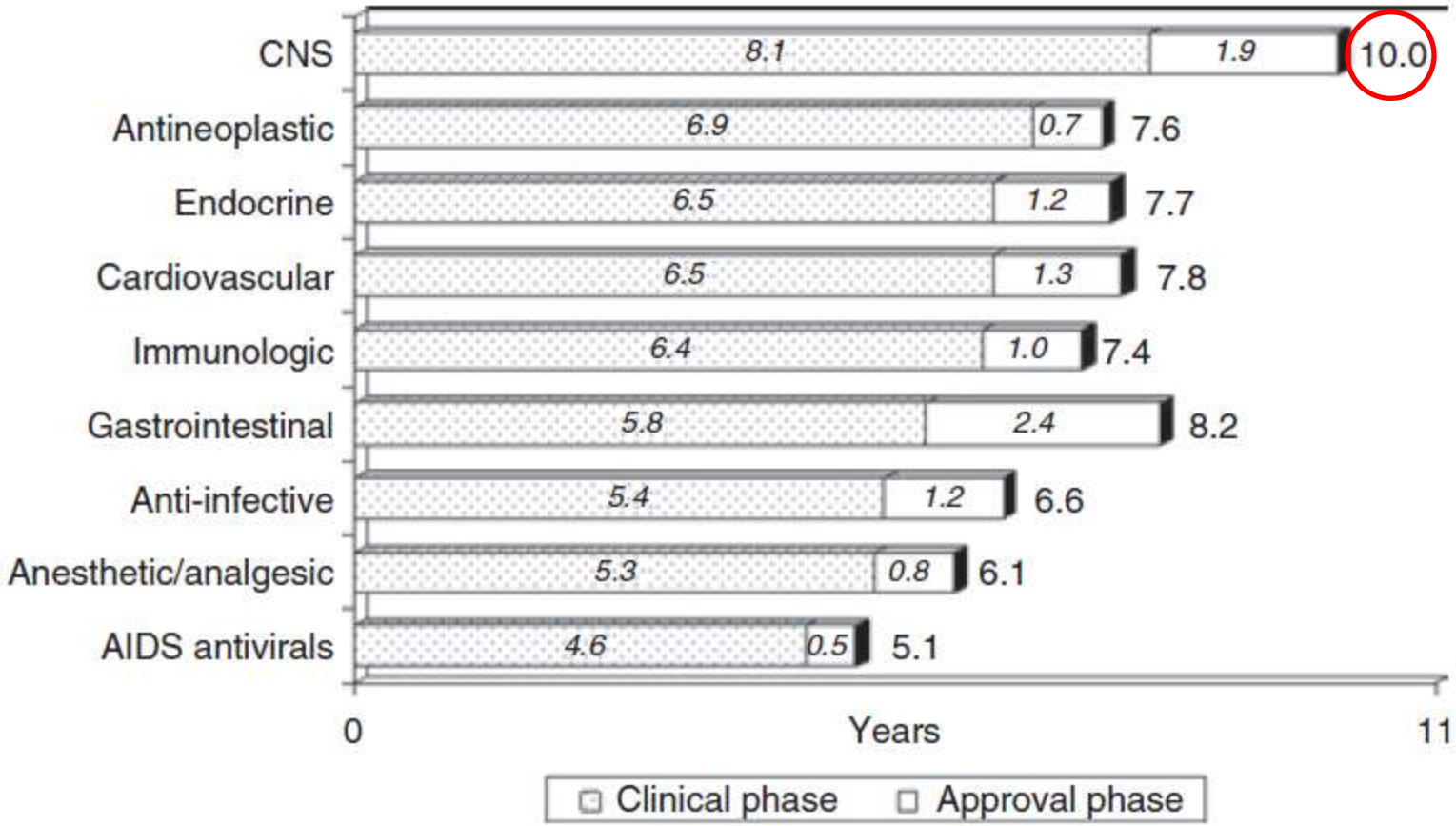
Through June 2009.

CNS, central nervous system; GI, gastrointestinal; RR, regulatory review.

BIOTRIAL

DiMasi et coll. Clinical Pharmacology & Therapeutics 2010

Duration of development



Kaitin & DiMasi Clinical Pharmacology & Therapeutics 2011

New Pharma CNS Paradigm