Non-Clinical and Clinical EEG tools. How they translate and can be scaled to clinical practice.

Alain PATAT, MD

Biotrial

Club Phase 1

17ème Annual Meeting

Paris, 05 April 2018

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Outline

- Introduction: Use of biomarkers
- EEG & ERPs as biomarkers for disease identification and drug development
- Examples of use of spontaneous EEG & ERPs
- Example of use of sleep EEG
- Conclusion

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Translational Biomarkers

BIO 2016 largest survey 9,985 transitions and 7,455 drugs

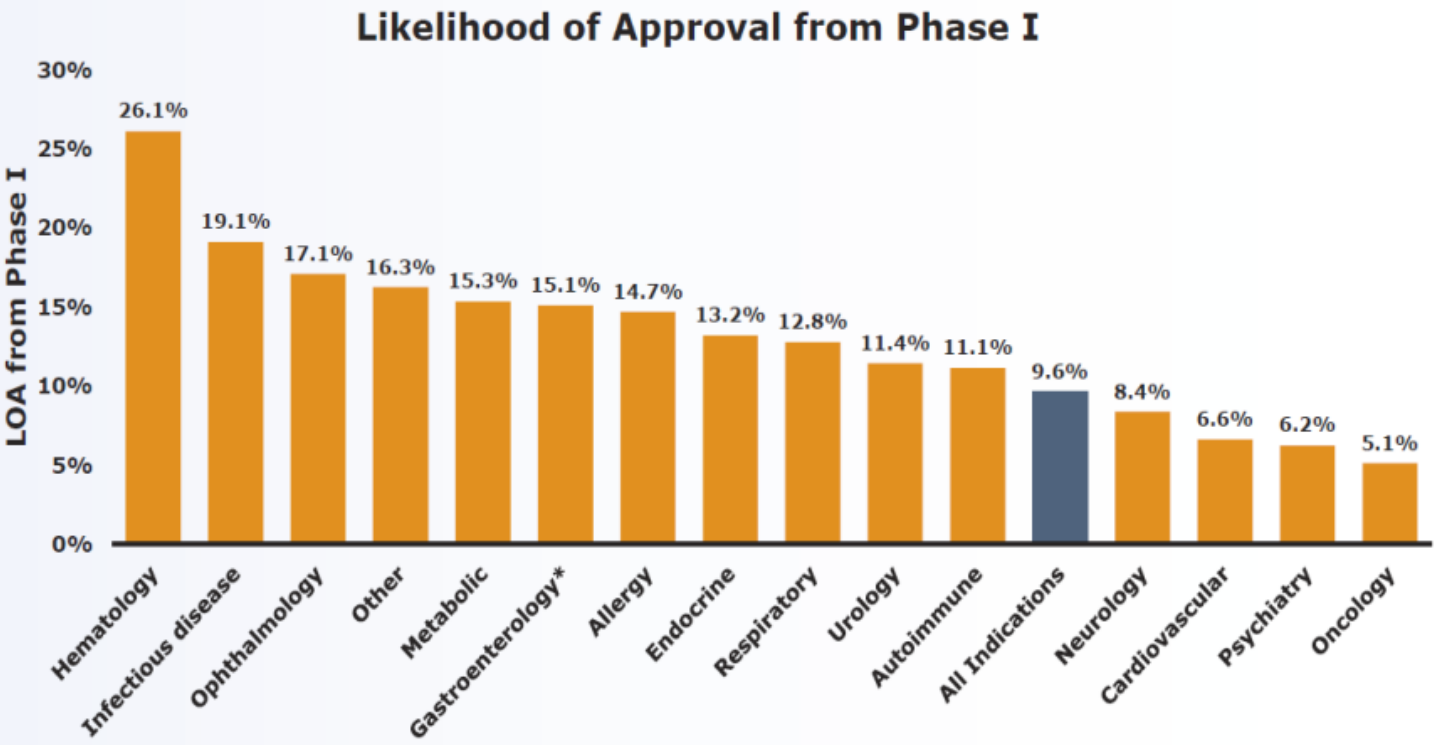

Figure 2a. Chart of LOA from Phase I, displayed highest to lowest by disease area.

David W. Thomas et al. 2016

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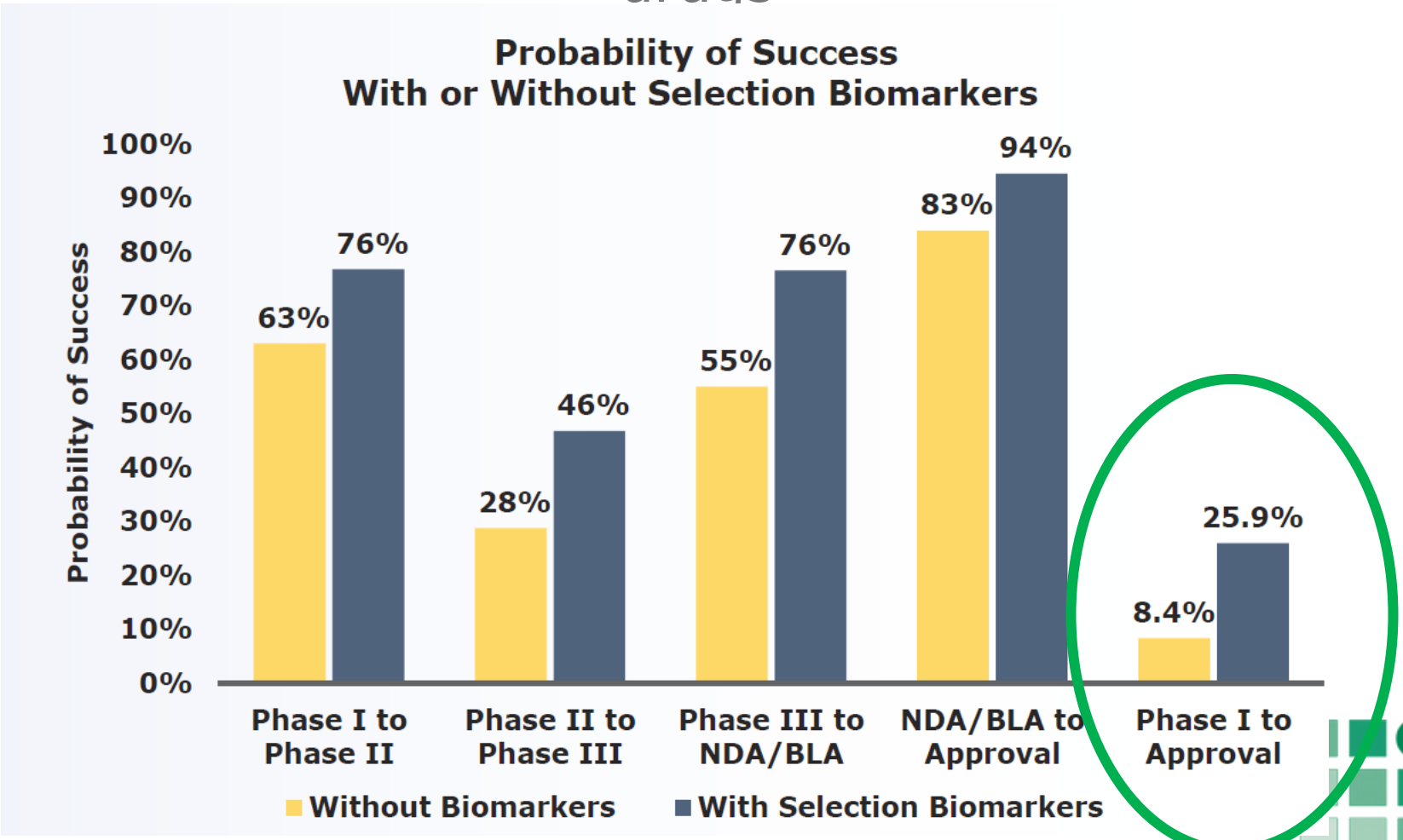
Translational Biomarkers

BIO 2016 largest survey 9,985 transitions and 7,455 drugs



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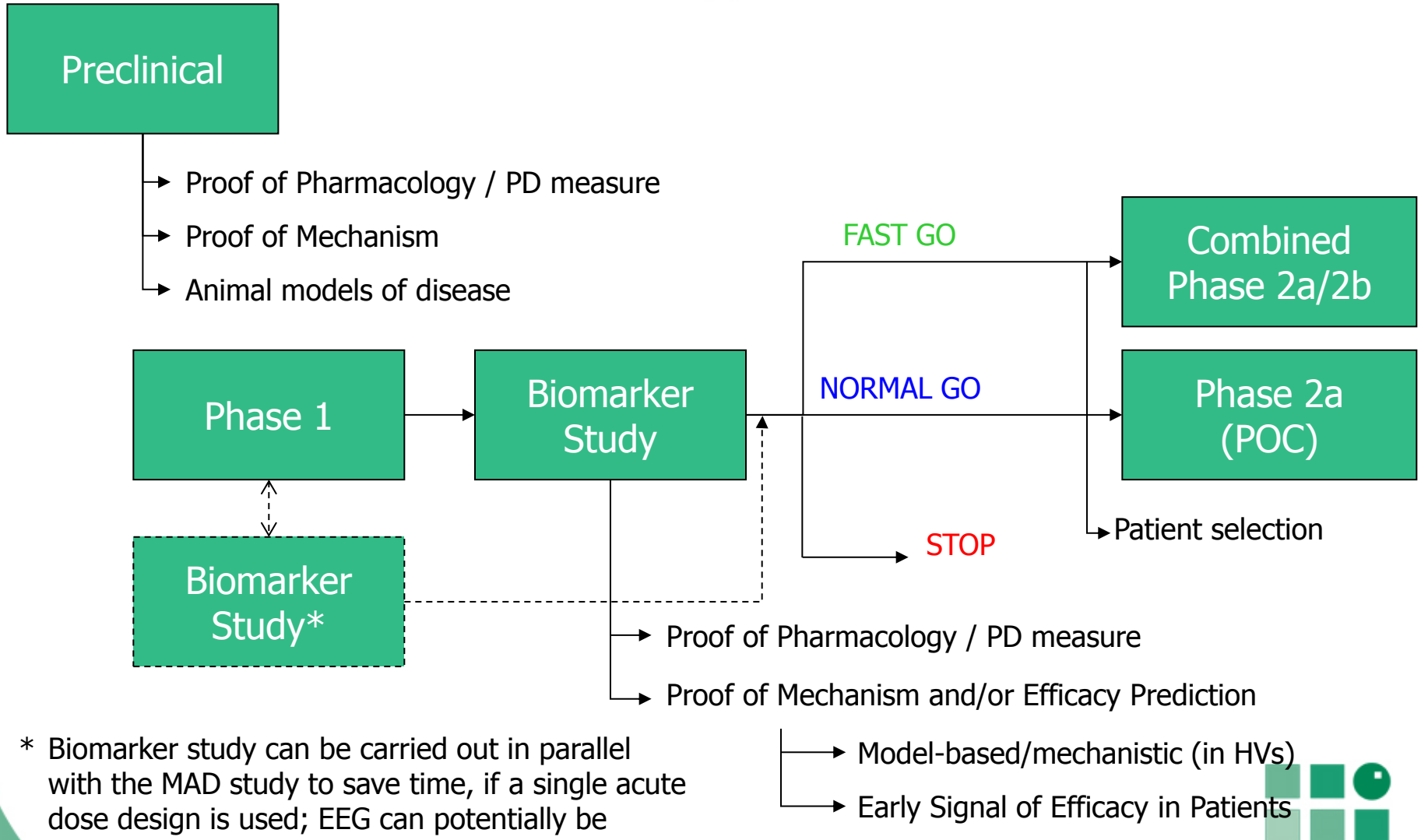
Utility of Biomarkers in Early Drug Development



* Biomarker study can be carried out in parallel with the MAD study to save time, if a single acute dose design is used; EEG can potentially be integrated in the Phase 1 (SAD or MAD) studies;

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Impact on Both Discovery and Development
Bridging Discovery and Development

Discovery

- Identify biomarkers for use in early clinical studies
- Improve predictability of animal models and cell systems
- Evaluate clinical relevance of targets
- Determine biomarker response at pharmacology active doses

Development

- Biomarkers can be used to:
  - Show early Proof-of-Biology
  - Guide dose selection in humans
  - Predict toxicity
  - Characterize exposure-response
- Clinical experimental models
- Selected exploratory studies
- Smaller and shorter POC studies

- **Shortened cycle time**
- **Higher success rate**
- **Early identification of probable failures**
- **Reduced risk**
- **Higher quality candidates**
- **Increased value of compounds**

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CNS Biomarkers & Their Utility

- **Examples of CNS biomarkers**
  - Peripheral or CSF wet markers (neuromediators or metabolites, enzyme reuptake inhibition or enzyme inhibition)
  - Electrophysiology (qEEG, ERPs, PSG, SEM…)
  - Psychomotor performance and cognitive functions
  - Brain imaging (MRI, fMRI, PET)
- **Use of CNS biomarkers in Early Development**
  - Translation from animal to human (dose selection)
  - Time course of central effect (optimize dosage regimen)
  - Predictivity of clinical efficacy (or safety)

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Use of cortical EEG as a Biomarker in drug development

- **EEG (oscillations)** is an old technique, discovered by Hans Berger in 1929, which improved since.
- Electrode numbers have increased from the initial single bipolar montage up to a high 256 electrodes density (improving source localisation and allowing connectivity measures)
- However, a limited number of electrodes is often sufficient for drug profiling using **EEG** which has been widely used in CNS drug development especially using spectral analysis: Fink (sixties), Itil (seventies), Hermann & Saletu (eigthies)
- Portable & cost-effective technique
- Applicable to animals with telemetry (translational tool)

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Utility of EEG as a CNS Biomarker in Drug Development

- **qEEG has as a number of characteristics of an "ideal" biomarker for CNS active compounds**, since:
  - recording and analysis techniques are relatively **unexpansive and broadly available preclinically and clinically**
  - it is continuous, objective, repeatable, reproducible, translatable and sensitive
  - it can be easily included in early clinical studies to measure CNS **pharmacological activity & neuronal function** and by inference **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

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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

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The fall and rise of EEG as a CNS biomarker

- However, there is a recent revival of the use of EEG as a CNS biomarker in drug development due to improved capabilities linked to technical advances:
  - **Improved EEG recording equipment** enables easier incorporation into clinical studies, **increased bandwidth (gamma), 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 to better address assessment of connectivity and neural networks

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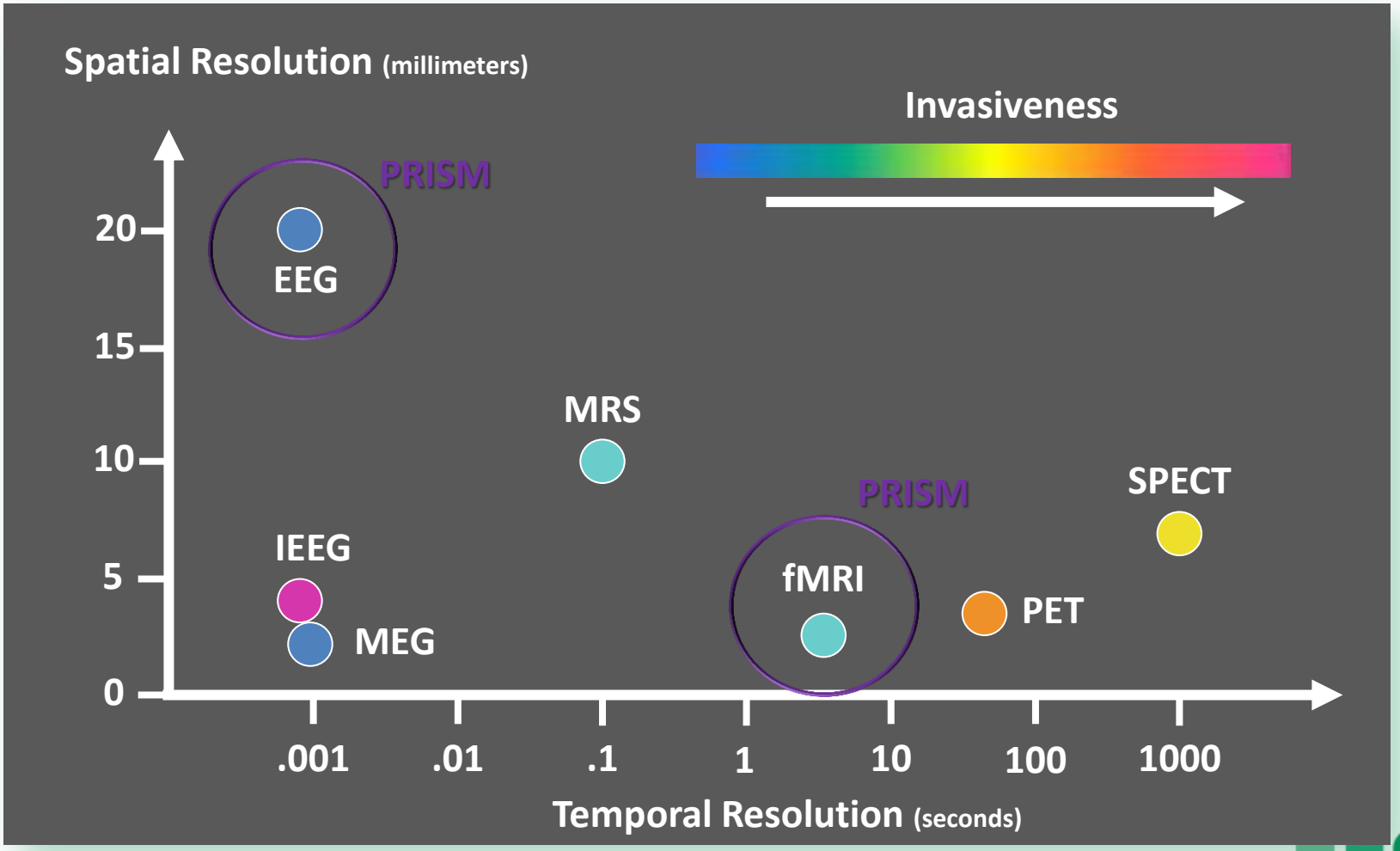
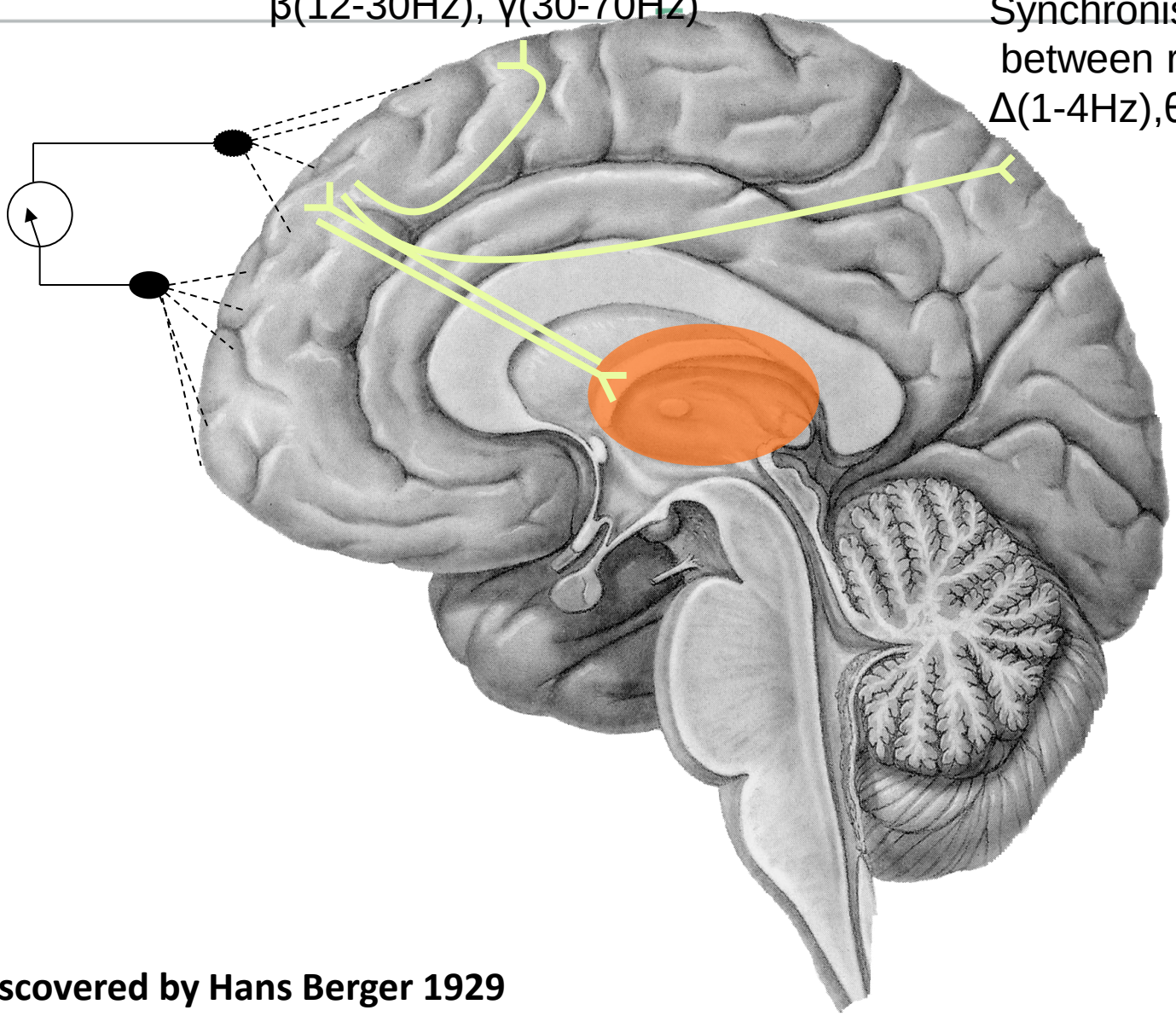
Different spatial and temporal resolutions



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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EEG (Oscillations)

- Detects the **summation of potentials** in the vicinity of surface electrodes through the scalp and skull (in humans) or at the cortex level (animals).

  - Oscillations dynamics (qEEG using frequency spectral analysis) is used to pragmatically identify patterns of temporal or spatial changes associated with :

    - a **state** (awake eyes open/closed, asleep, drowsy)
    - a **drug**
    - a **phenotype** for alpha magnitude and now COMT val15met polymorphism,
    - a **pathology**: Alzheimer, schizophrenia etc.

  - Scales very well with animals

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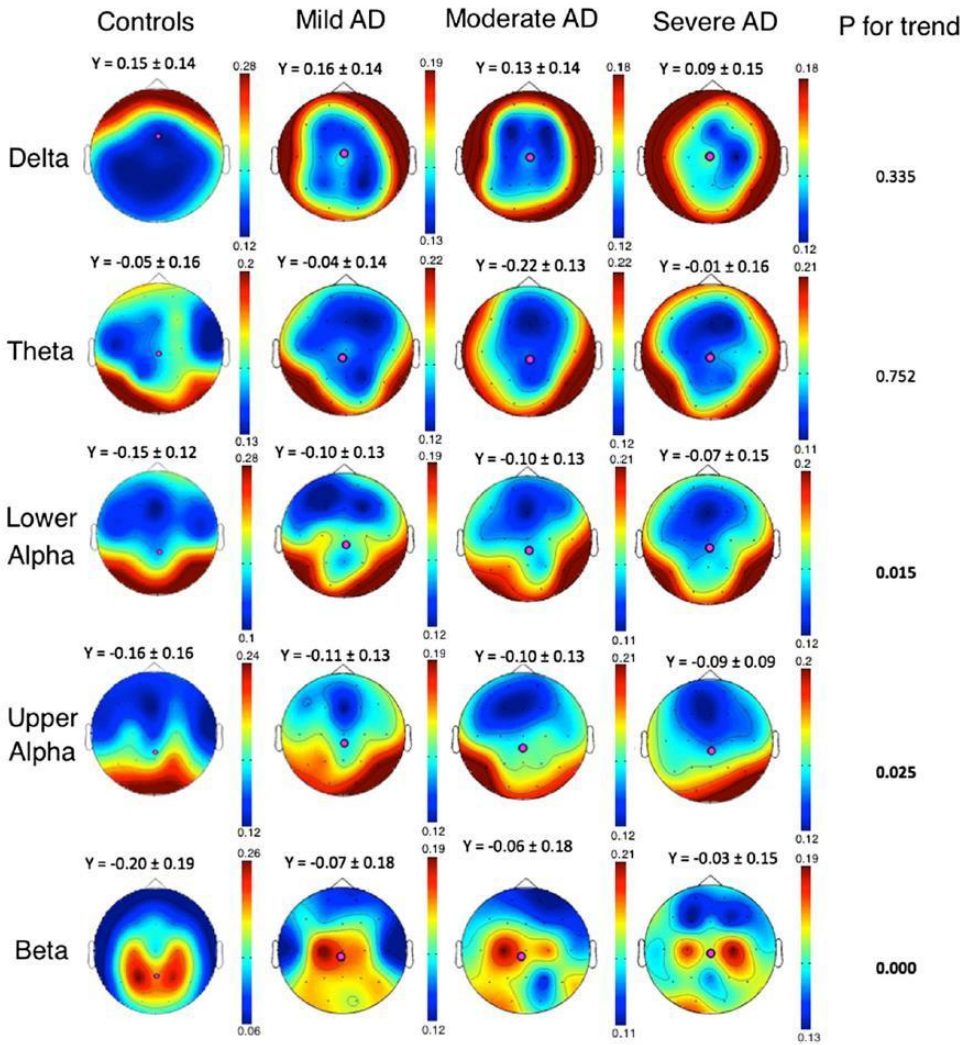
EEG as Biomarker in AD

qEEG advantages over other BM and Bioimaging

- ✓ Measures oscillatory electrical brain activity and captures dynamical processes at the macroscopic scale
- ✓ Relatively easy to deploy in Clinical trials
  - ✓ Inexpensive
  - ✓ Non invasive
  - ✓ Repeated
  - ✓ Possibly remote



Van Straaten et al Alzh Res Ther 2014

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Evoked Related Potentials (ERPs)

- **Potentials of very small voltage, generated in response to specific event or stimulus overimposed to oscillations** corresponding to the sum of **Exitatory Post Synaptic Potentials** (EPSP) from 100,000-1,000,000 pyramidal cells firing
- First 100 msec termed « **sensory** » or « exogenous » and later potentials « **cognitive** »or « endogenous »:
- Various ERPs
  - **P50**: strength of inhibitory pathways exploited for **auditory gating**
  - **N200 (N2a=MisMatchNegativity)**: **Unconscious reaction when a rule is violated** elicited by any discriminable change
  - **P300: Cognitive potential** when a deviant stimulus is detected consciously with processing exploited in auditory oddball
  - **Auditory Steady State Response (ASSR)** with click stimuli at 4OHz
- Key to ERP is **time resolution** (in the msec range) & **location of potentials**, described with their validation (often one group or even one electrode being better as generating a greater potential)
- ERPs are more complex to adapt to animals particularly rodents

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ERPs: Close paradigms, Big difference

- Both auditory oddball (**P300**) and **M**is**M**atch **N**egativity (**N200**) are based on the **detection of a rare deviant sound** from a frequent one.

- For P300, this is a **conscious task processing** with a behavioural response (key press, counting etc) when a deviant stimulus is detected consciously, as for MMN no response is expected and distractor used (e.g. cartoon).

- MMN is **automatic and preattentional** occurring around 200 msec

P300 is a **cognitive potential** occurring from 300 msec and onwards

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Event Related Potential

Mismatch Negativity (MMN)

Auditory oddball stimuli

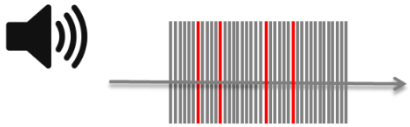
510 standard (frequent 85%), 1000 Hz, 50 ms

90 deviant (rare 15%) , 2000 Hz, 50 ms

ISI = 600 ms

Eyes closed (6 min)

+



Total of 1500 tones with :

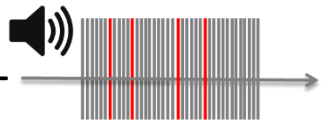
1200 frequent tones

150 pitch deviants and 150 duration deviants

Eyes open (12 min)

+

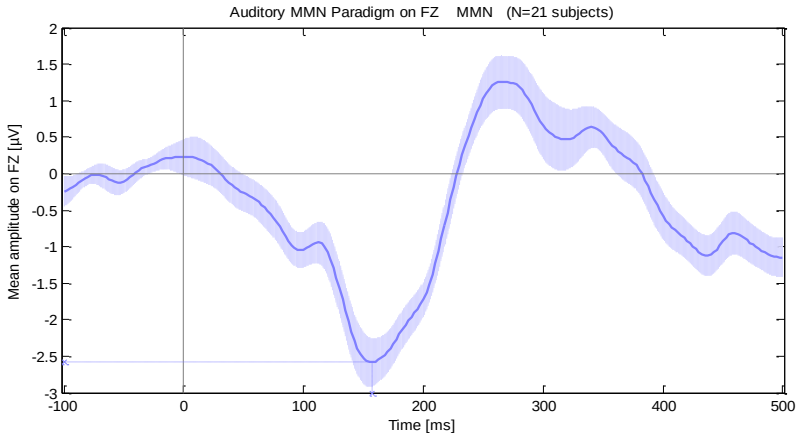
+



Watching silent video

Duration : 18 min

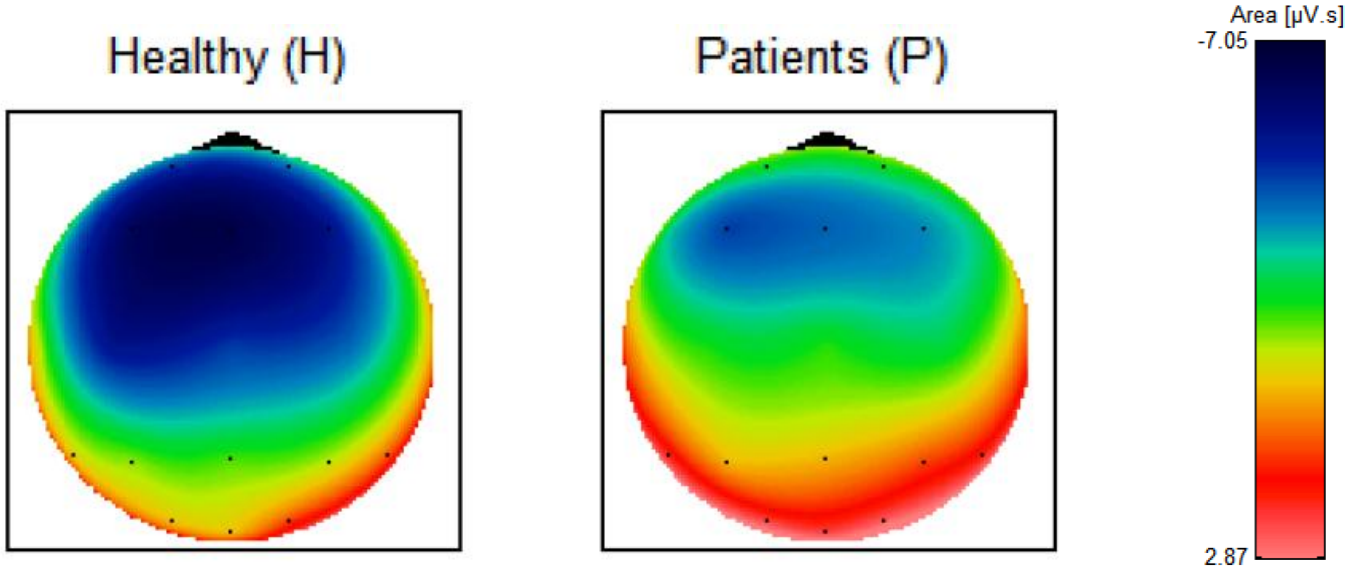
- MMN is characterized by the difference in the brain response between frequent tones and deviant tones
- Average ERP is built for frequent and deviant tones
- Difference between frequent and deviant is calculated
- On average difference, morphological descriptors (quantitative) are derived:
  - Amplitude
  - Latency
  - Area under the curve (MMN)



Event Related Potential

Mismatch Negativity (MMN)

Difference between healthy subjects (n=32) and schizophrenic patients) (n=12)



MMN located in Fronto-Central area
Schizophrenic patients show an attenuation of the MMN

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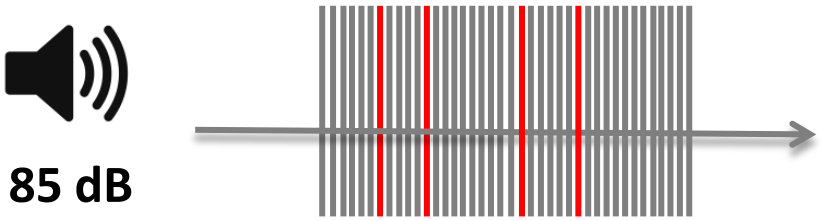
Event Related Potential

Auditory P300

The P300 is a large and positive component that peaks approx 300 ms after onset of a rare stimulus - Duncan (2009)

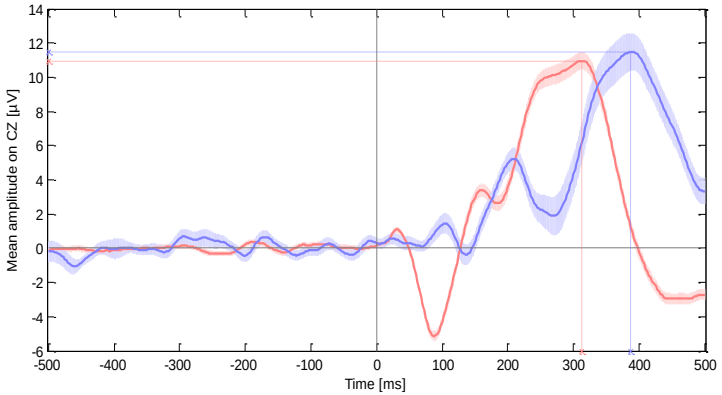
Auditory oddball stimuli

Frequent : 85%, 500 Hz, 10 ms
Rare: 15% (n=30-40), 2000 Hz, 10 ms
ISI = 1200 to 1900 ms



Subject : must count the rare sounds

Duration : 4 to 9 min



Grand average ERP from **visual (blue)** and **auditory (red)** oddball paradigms on Cz. Mean and SEM. The P300 wave's maxima are marked by dashed lines. Visual P300: 11.4772µV at 387.5ms (n=21).
Auditory P300: 10.9571µV at 312.5ms (historical data, n=124).

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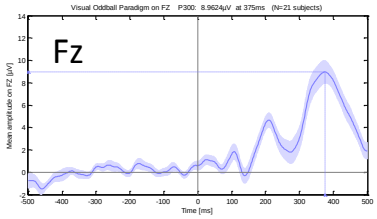
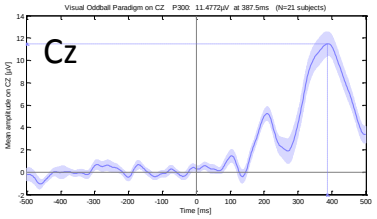
Visual Oddball (P300)

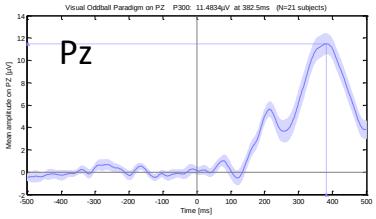
Pilot study results

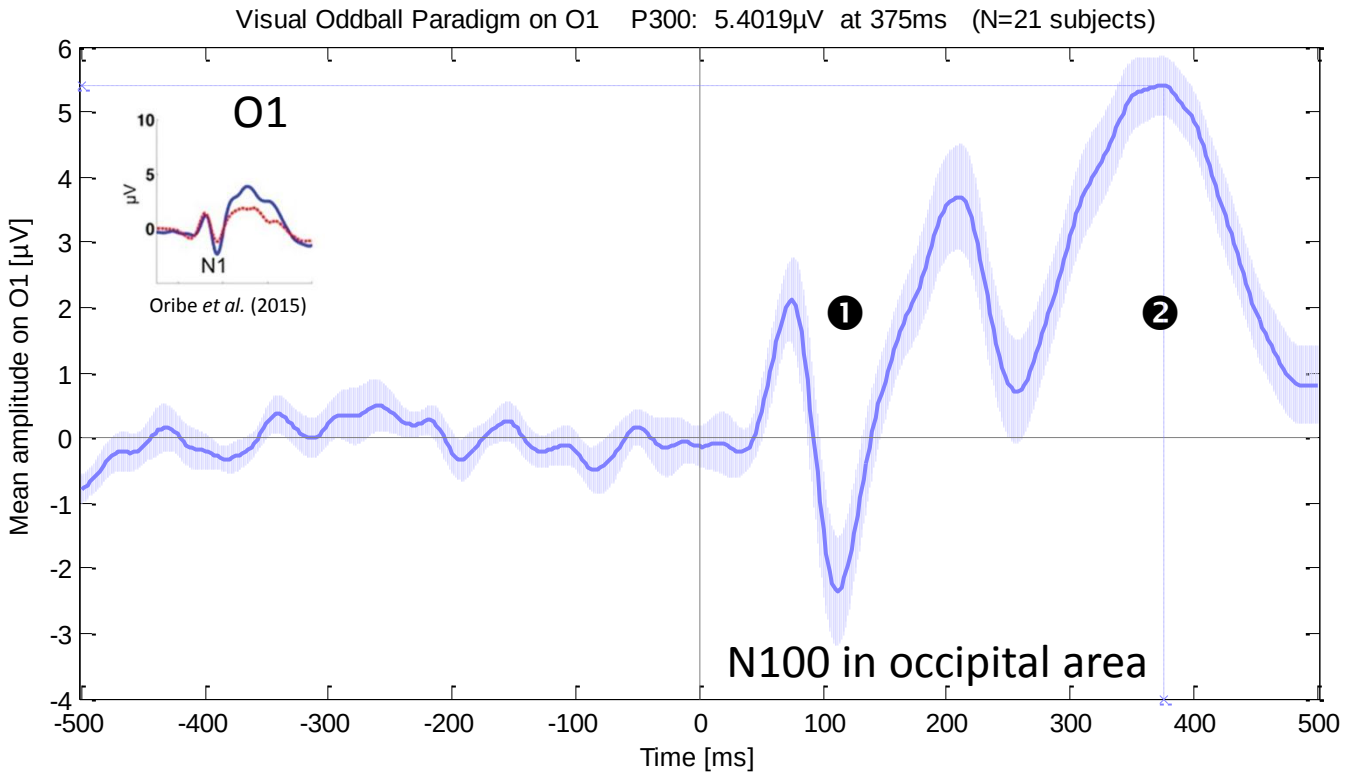
PRISM

Results from pilot study – ERP flat maps

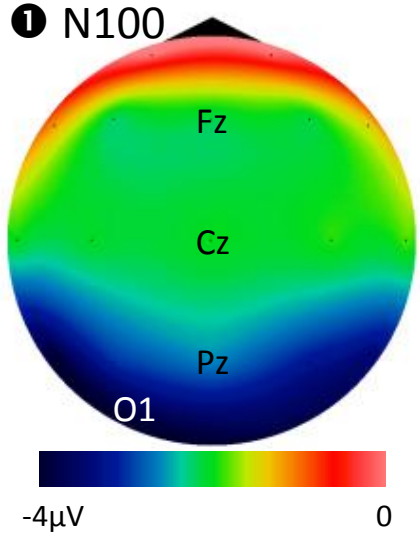




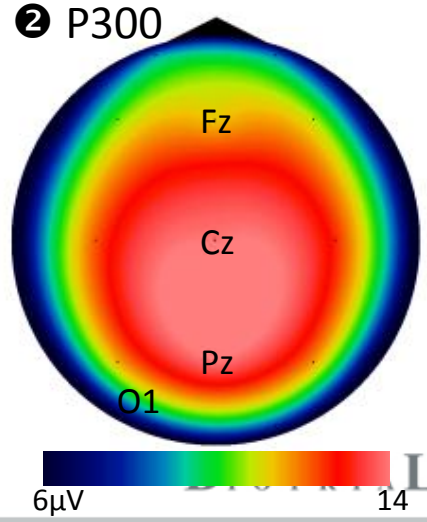




❶ N100



❷ P300



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

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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Hypnotic Drugs

- Ideal example of an easy and validated use of CNS biomarkers to define active dose and safety profile
- **qEEG**: time course of effect (increase delta and theta, decrease alpha and fast beta and gamma, increase beta 1 for benzodiazepine)
- **Latency to Sleep Onset**: Multiple sleep latency test
- **PSG:** define sleep efficiency and profile
- **Psychomotor and cognitive testing**: to define lack of residual effects
- Various models to sensitize effects on sleep onset and/or sleep maintenance (post nap effect, phase advanced, noise induced (for sleep maintenance only))

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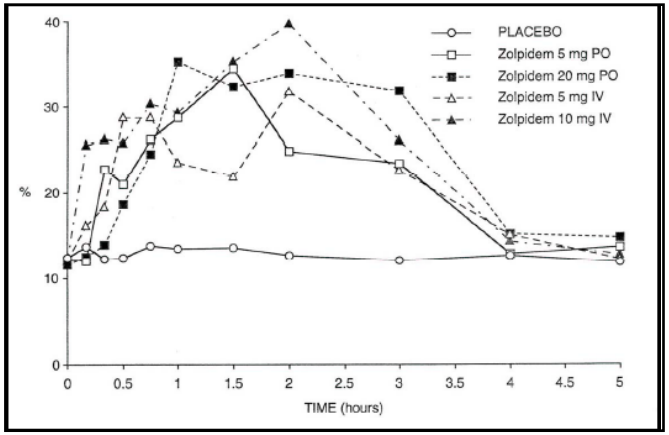
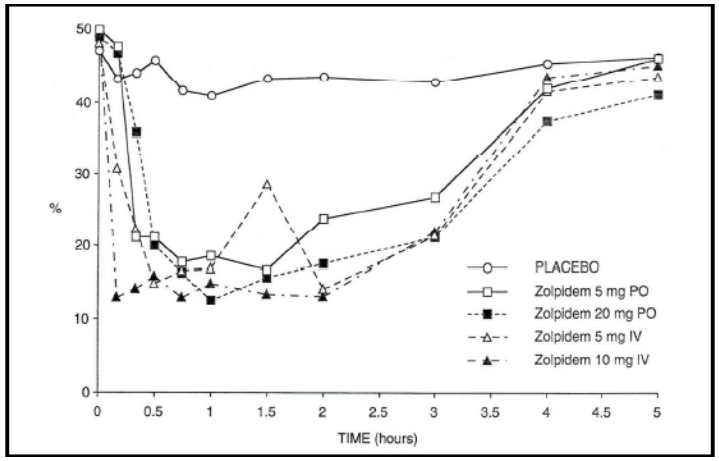
PD effects of oral and iv zolpidem administration in 12 healthy subjects

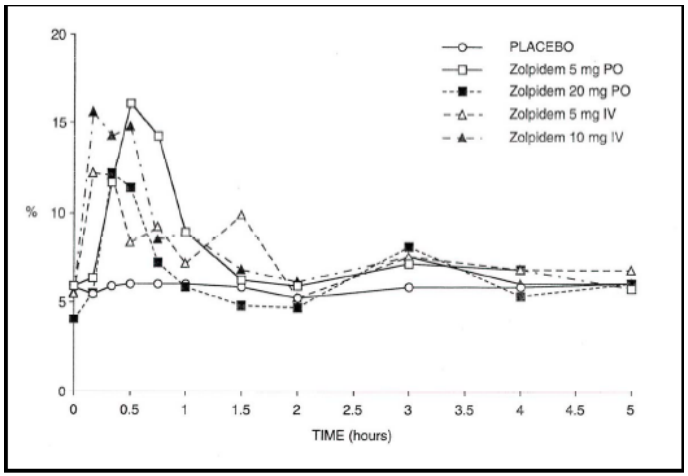
DELTA ENERGIES



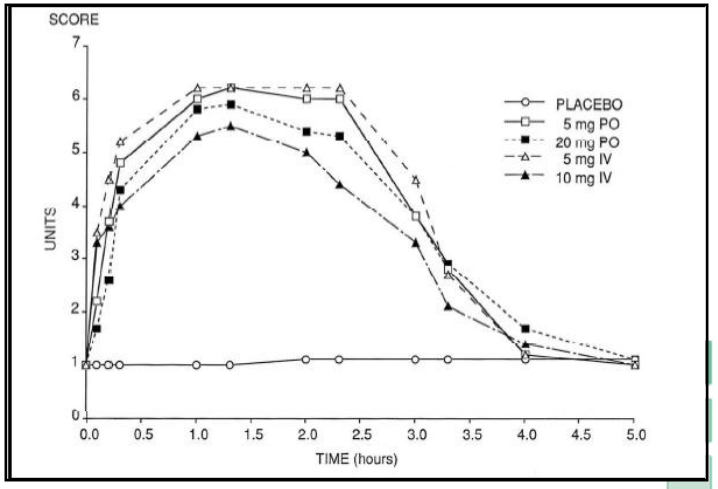
ALPHA ENERGIES



BETA1 ENERGIES



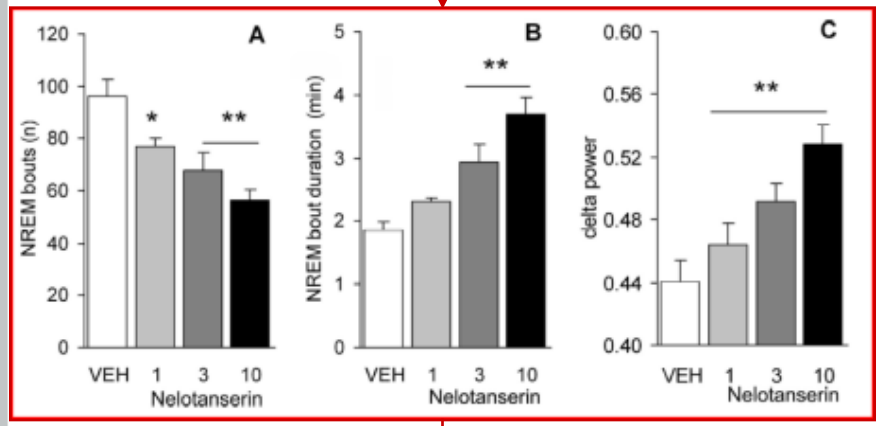
STANFORD SLEEPINESS SCALE



Patat et al, Psychopharmacol, 1994; 114 : 138-146

Delta sleep and 5-HT2a receptor

Rat study : **Dose-dependent increases in NREM sleep consolidation and delta power**



0022-3565/10/3321-1–10$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
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JPET 332:1–10, 2010
Vol. 332, No. 1
160994/3548234
Printed in U.S.A.

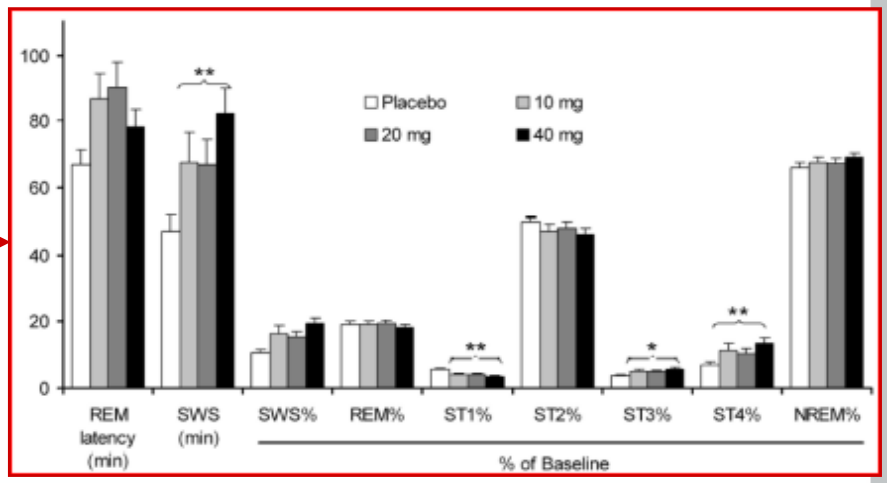
Nelotanserin, a Novel Selective Human 5-Hydroxytryptamine$_{2A}$ Inverse Agonist for the Treatment of Insomnia[S]

Hussien A. Al-Shamma, Christen Anderson, Emil Chuang, Remy Luthringer, Andrew J. Grottick, Erin Hauser, Michael Morgan, William Shanahan, Bradley R. Teegarden, William J. Thomsen, and Dominic Behan

Arena Pharmaceuticals, Inc., San Diego, California (H.A.A., C.A., E.C., A.J.G., E.H., M.M., W.S., B.R.T., W.J.T., D.B.); and FORENAP Pharma, Rouffach, France (R.L.)

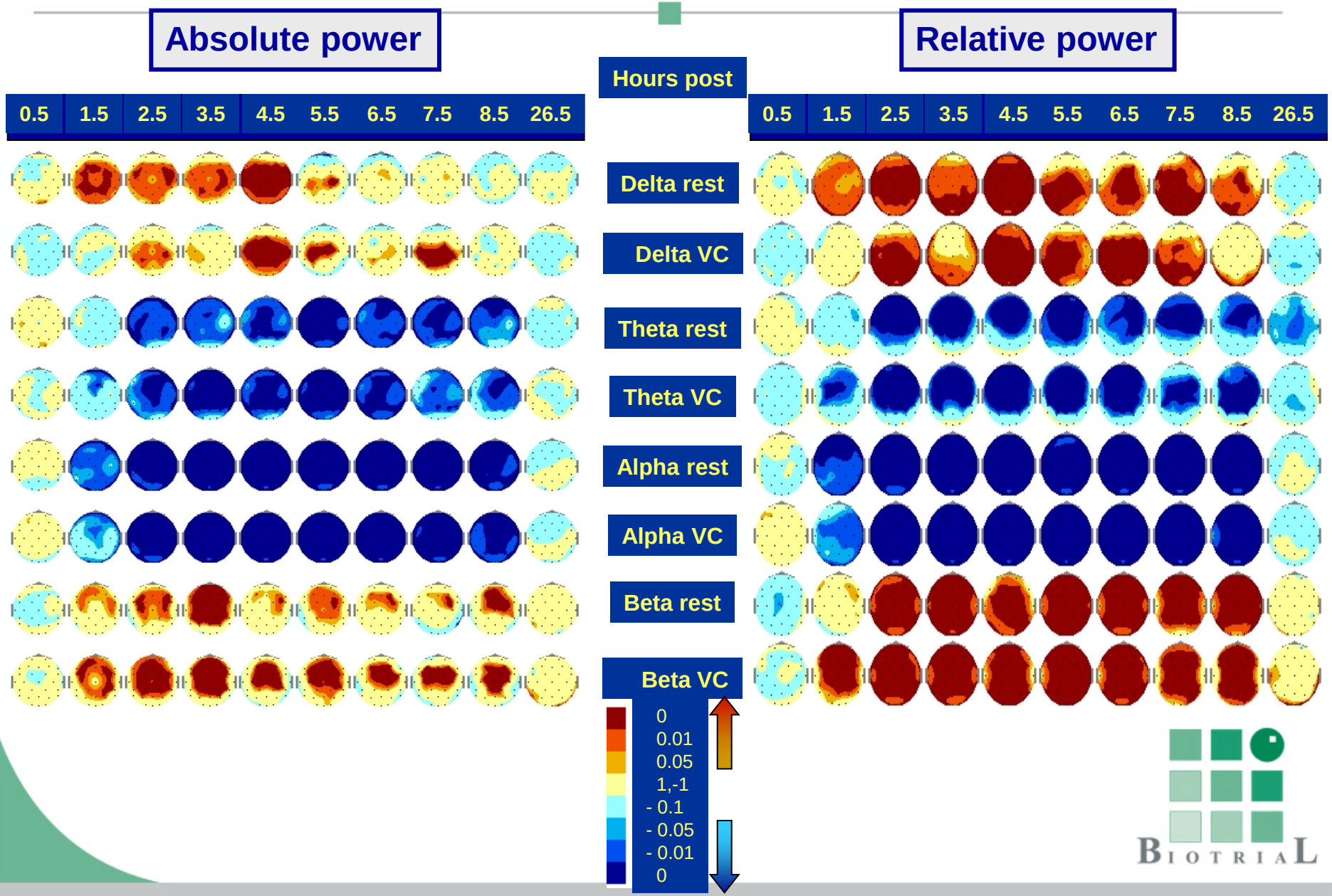
Received August 27, 2009; accepted October 19, 2009

Effects of a single bedtime dose of nelotanserin on sleep architecture in the post-nap sleep model of insomnia.



Healthy subjects : **Dose-dependent increases in SWS**

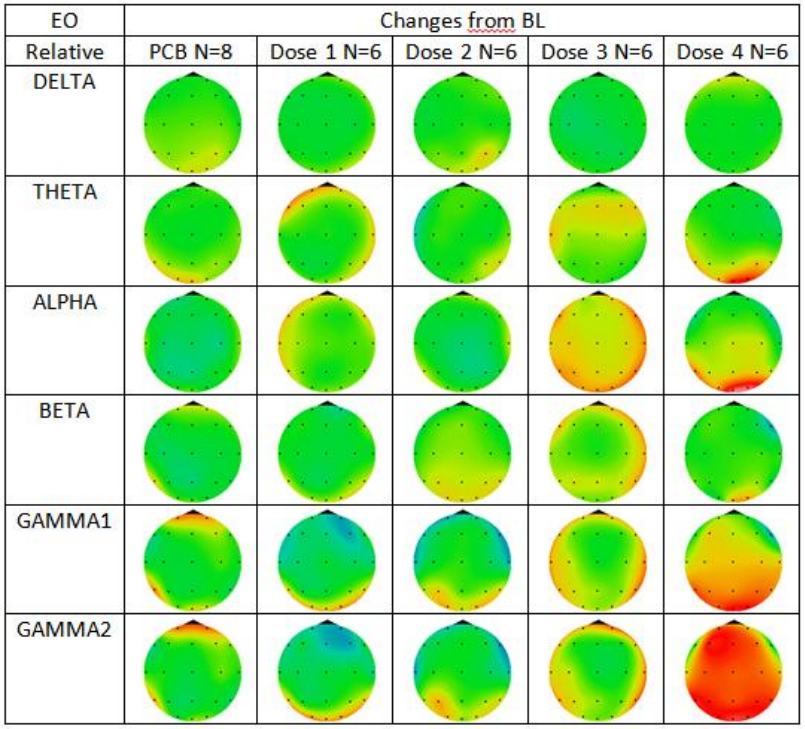
Lorazepam (2 mg) vs placebo in young healthy men



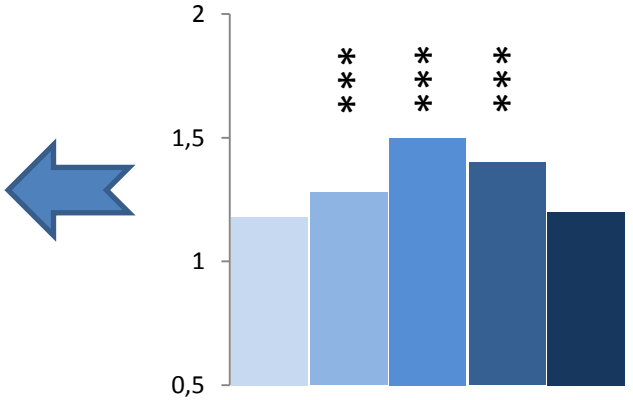
EEG in SAD & MAD of a drug to treat neurodegeneration and restore cognitive function in Alzheimer's disease patients

Gamma Power

- First in human SAD trial conducted at Biotrial CPU in cohorts of 8 subjects (6 active & 2 placebo): qEEG add-on (baseline and 1h post dose)
- Change in relative power in standard frequency bands (eyes open)
- Consistent with animal data

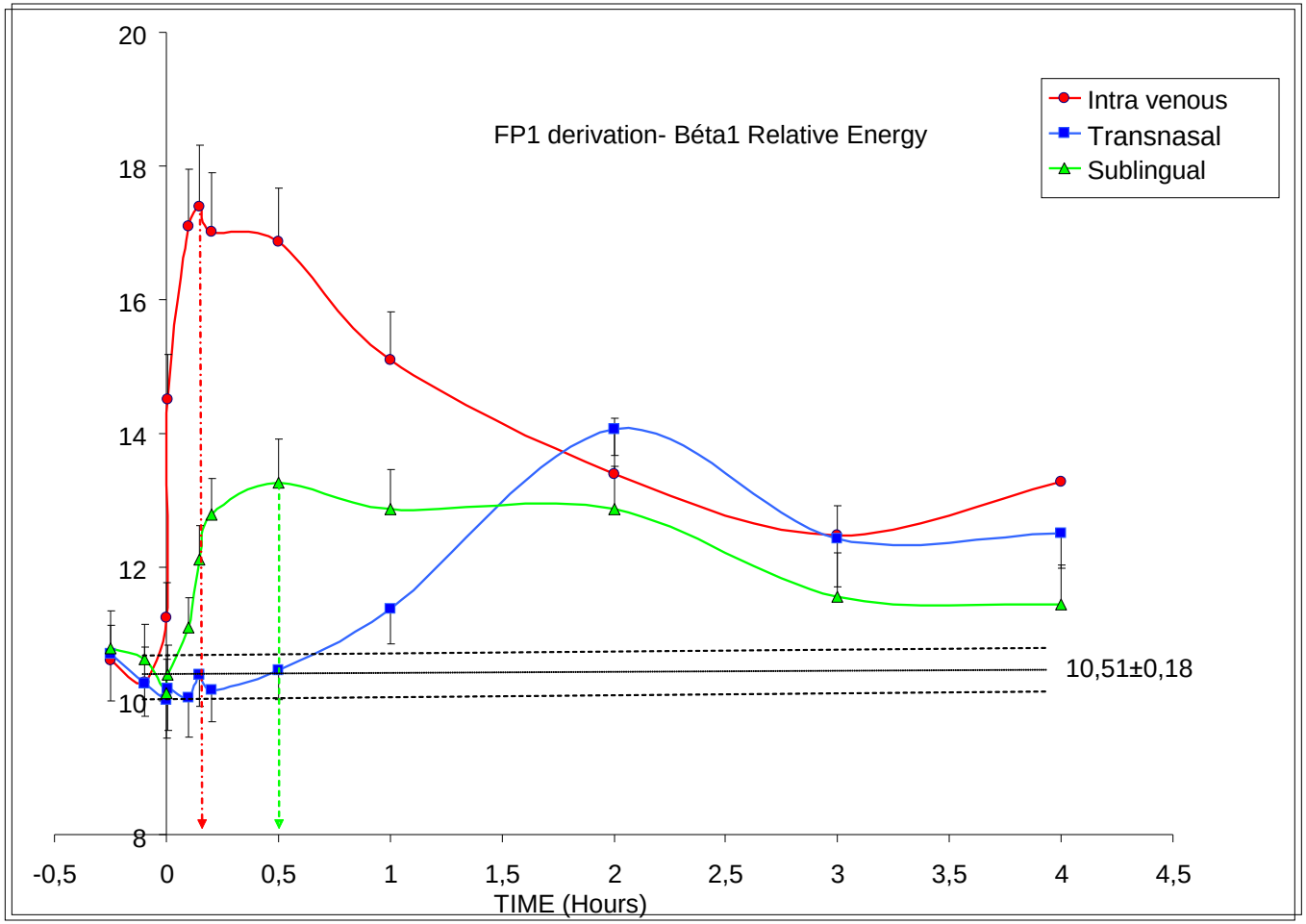


Effect on Gamma (animal)



BIOTRIAL

qEEG: β1 in FP1 with 3 formulations of alprazolam in 12 subjects (IV, transnasal & sublingual)



BIOTRIAL

Evidence of target engagement in a multiple ascending dose study with BNC210, an α7 nicotinic Acetylcholine Receptor (nAChR) negative allosteric modulator (NAM) in development for the treatment of anxiety disorders

- **BACKGROUND:** BNC210 is a **negative allosteric modulator (NAM) of the α7 nicotinic Acetylcholine Receptor** in development for the treatment of anxiety disorders.

- **STUDY DESIGN:** Randomised, double-blind, placebo-controlled, MAD oral doses BID for 8 days study in healthy subjects: Cohorts 300, 600 and 1200 mg/day with 8 subjects (6 active & 2 placebo) & **2000 mg/day** in **30 subjects** (24 active & 6 placebo) for the nicotine shift assay.

- **TARGET ENGAGEMENT METHOD - NICOTINE SHIFT ASSAY**

Quantitative EEG (qEEG) recordings were performed at screening, on D-1 (before dosing) and after 7 days of dosing with 2000 mg (6h after dosing)). Dose titrations of nicotine (from 0.5 to 2 mg) were administered by nasal spray (Nicorette®) 10' prior to recordings (2' eyes-closed). **The alpha-2 band (10-12.5Hz) of qEEG should increase after nicotine in a dose dependent manner**.

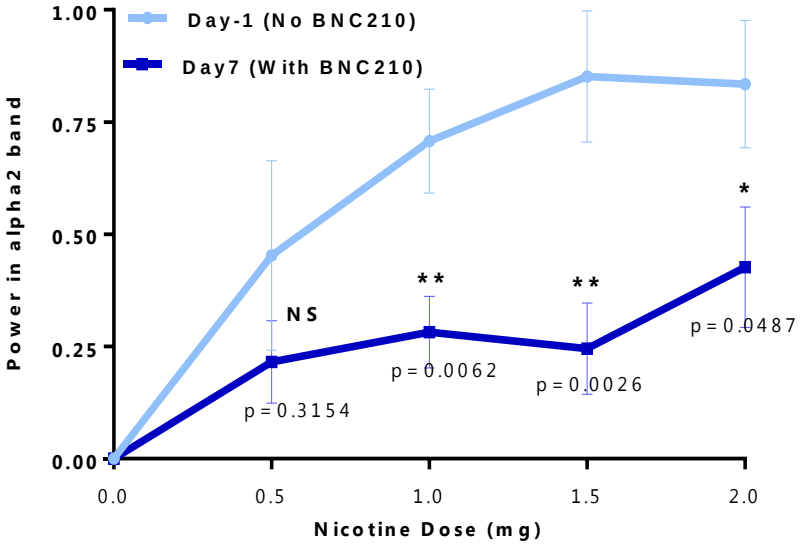
Subjects who produced a nicotine dose response at screening and on Day-1 were used for analysis in the nicotine shift assay (RESPONDERS)

Analyses of the nicotine shift assay compared nicotine dose response data on Day-1 (baseline before drug) with dose response data on Day 7 (steady state after 2000 mg BNC210)

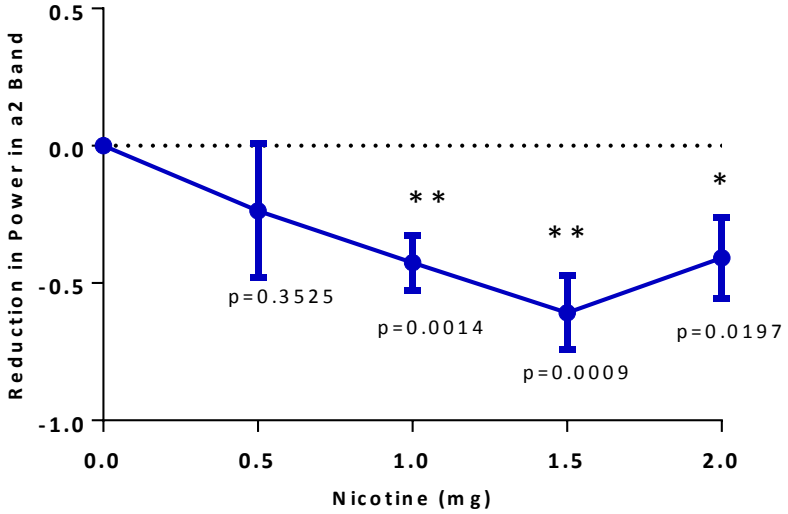
BIOTRIAL

Evidence of target engagement in a multiple ascending dose study with BNC210, an α7 nicotinic Acetylcholine Receptor (nAChR) negative allosteric modulator (NAM) in development for the treatment of anxiety disorders

Multiple doses of 2000 mg/day of BNC210 significantly reduced the peak height of nicotine responses on the α2 band measured using qEEG in 24 healthy subjects



Nicotine shift after multiple dosing of BNC210 for 7 days in 24 healthy subjects showing a significant reduction in a2 power amplitude compared to baseline (day -1)



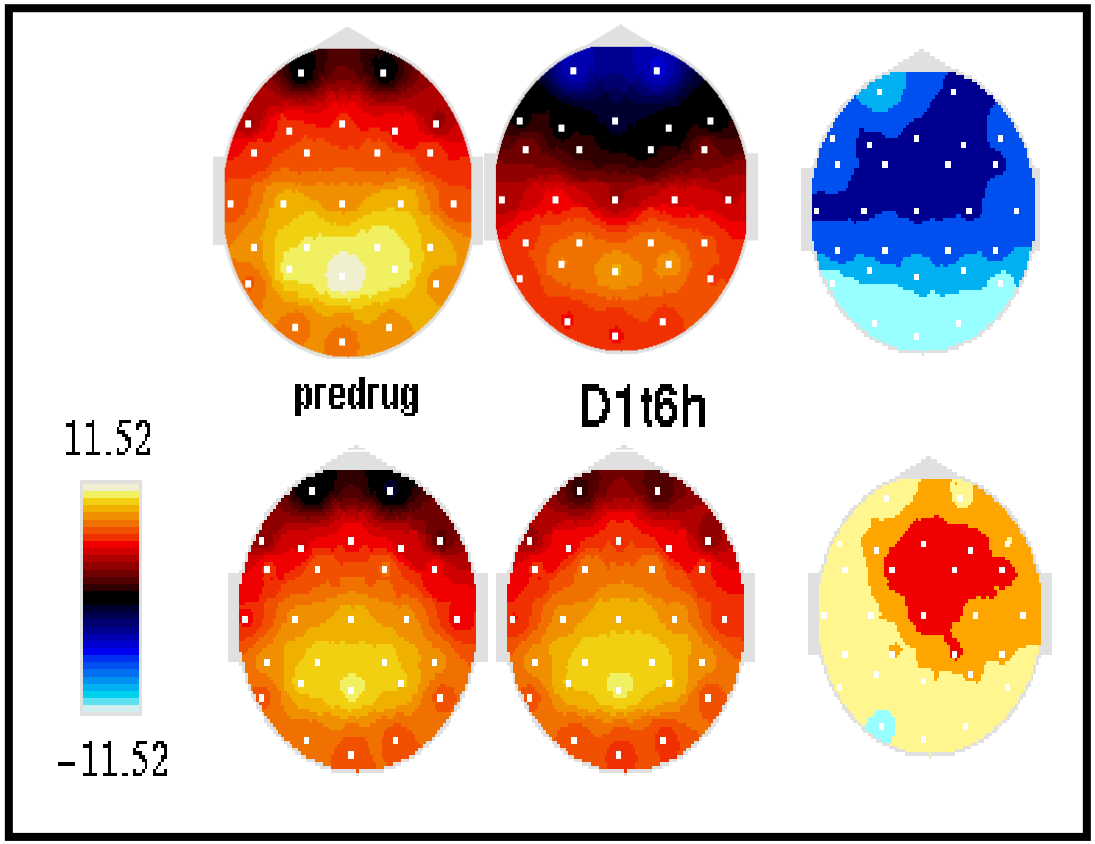
BIOTRIAL

Pharmacodynamic : P300 amplitude of auditory ERP after a single dose of Scopolamine and Donepezil

P300 amplitude : Scopolamine, an anticholenergic drug, significantly decreased P300 amplitude and donepezil, an acetylcholinesterase inhibitor, had the opposite effect

Scopolamine 0.5 mg SC

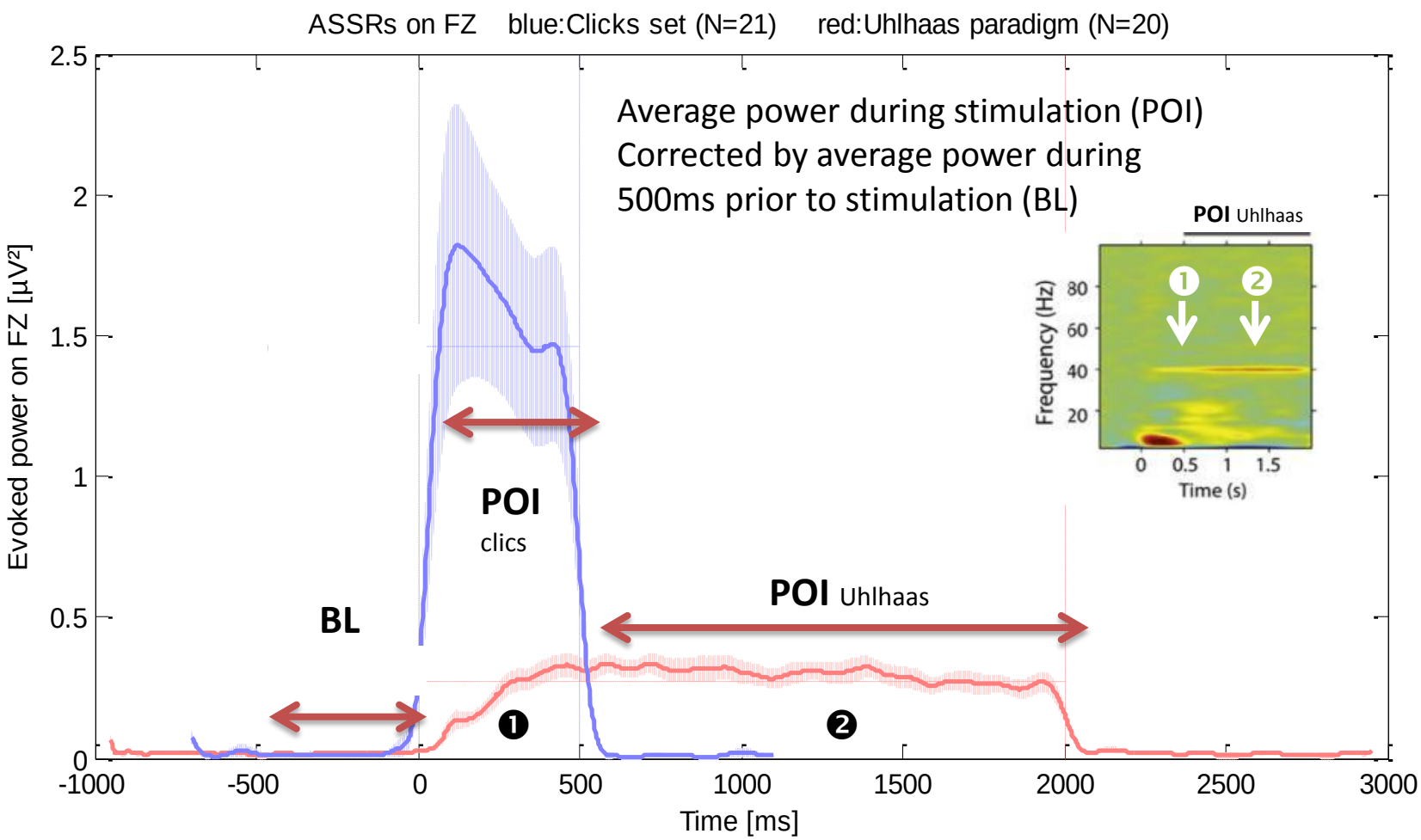
Donepezil 5 mg orally



BIOTRIAL

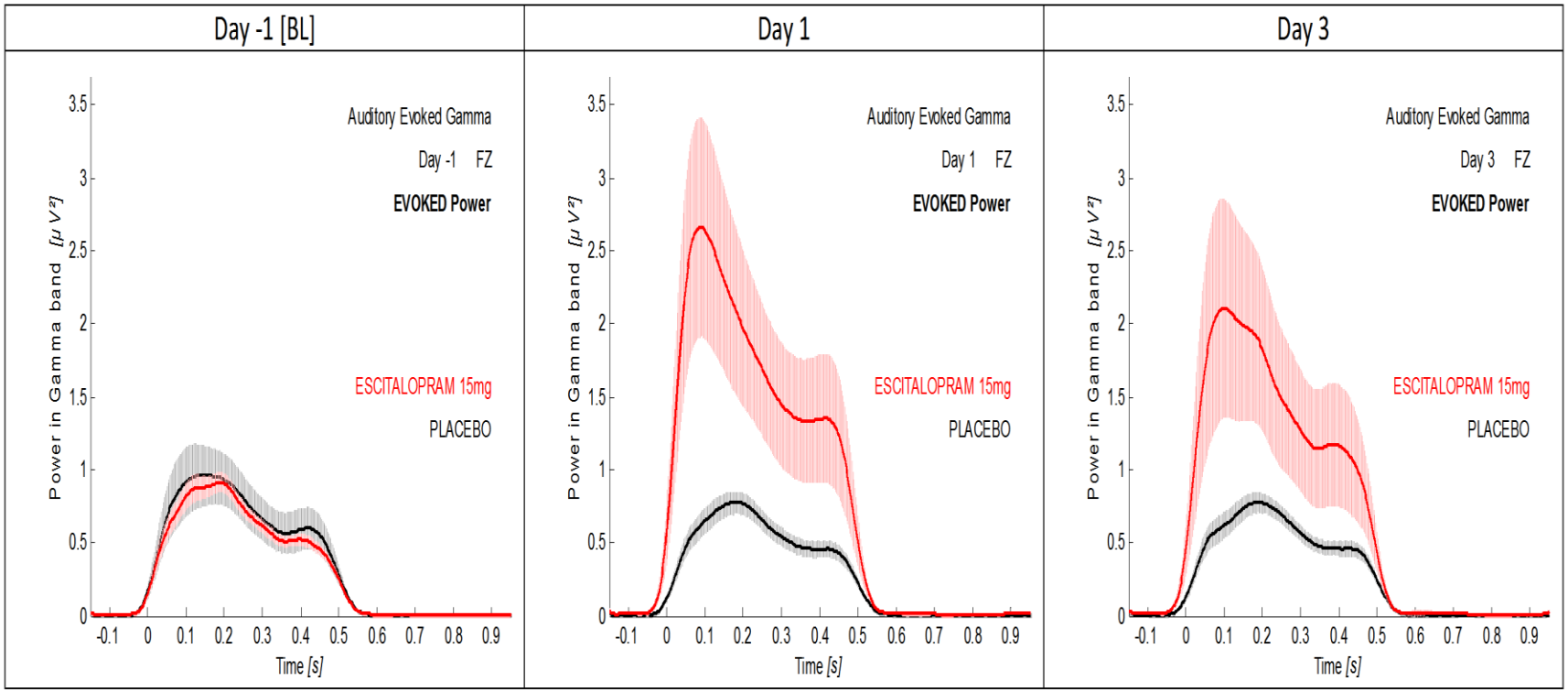
Auditory Steady-State Response (ASSR)

Parameters



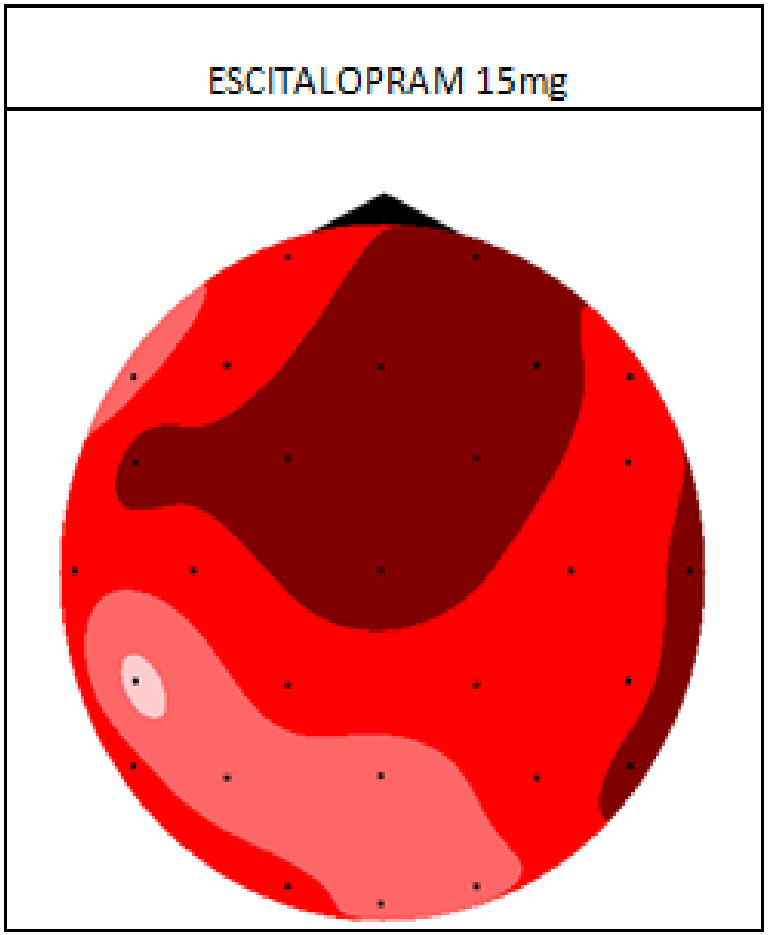
Effect of escitalopram 15mg/d on ASSR in 32 healthy male subjects

Fz : evoked gamma (35-45 Hz)

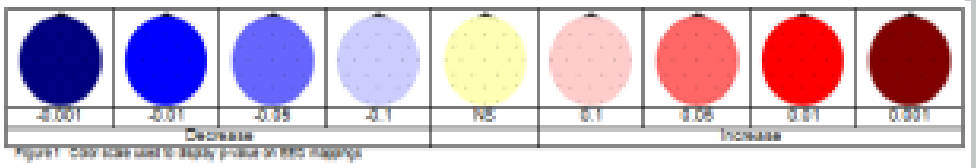


Escitalopram evoked gamma (ASSR elicited by clicks)

BRAIN MAPPING REPRESENTATION OF AUDITORY EVOKED GAMMA



Statistical comparison of absolute power (treatment v/s placebo)



BIOTRIAL

Sleep Studies

- Sleep is an important function of brain and during sleep many offline processing occurs (episodic and procedural memory consolidation, metabolic cleaning, etc).

- Sleep is **affected by most of CNS active drugs** and then sleep may contain **biomarkers of Mechanism Of Action which are silent during day**.

- Some examples are **biomarkers** of **antidepressant** (REM suppression and increase in REM latency) or **hypnotic drugs action**

- For a CNS-active drug, not studying its effects on sleep would be odd and was systematic in the past.

- Combined studies with daytime EEG and Polysomnography covers all aspects of CNS functioning

- Some vertical integration between species for elementary components although sleep structure varies between species.

BIOTRIAL

Rat electrocorticogram sensitivity matrix (light phase)

			Sleep Continuity	Sleep Architecture		
			Wake	REM sleep	Spindles (ST2)	Delta (SWS)
Glutamate	NMDA antagonists	MK-801	▲	▼	▼	▼
	Gly T1 inhibitor	SSR504734	▲	▼	▼	▼
	mGlu2/3 antagonist	LY379268	▲	▼	▼	▼
Acetylcholine	nAchR agonist	Nicotine	▲	▼	▼	▼
	mAchR antagonist	Pirenzepine	•	▼	•	•
	AchE inhibitor	Donepezil	▲	•	•	▼
Norepinephrine	Alpha 1 antagonist	Prazosin	▼	▲	•	•
	Alpha 2 agonist	Clonidine	▼	▼	▲	▼
	Beta 3 agonist	SR58611A	•	▼	•	•
	NET inhibitor	Desipramine	•	▼	•	•
Serotonin	5-HT1a agonist	Ipsapirone	▲	▼	•	▼
	5-HT2a antagonist	APD-125	▼	•	•	▲
	5-HT3 agonist	m-CPBG	▲	▼	•	▼
	5-HT7 antagonist	SB-656104	•	▼	•	•
	SERT inhibitor	Citalopram	•	▼	•	▼

BIOTRIAL

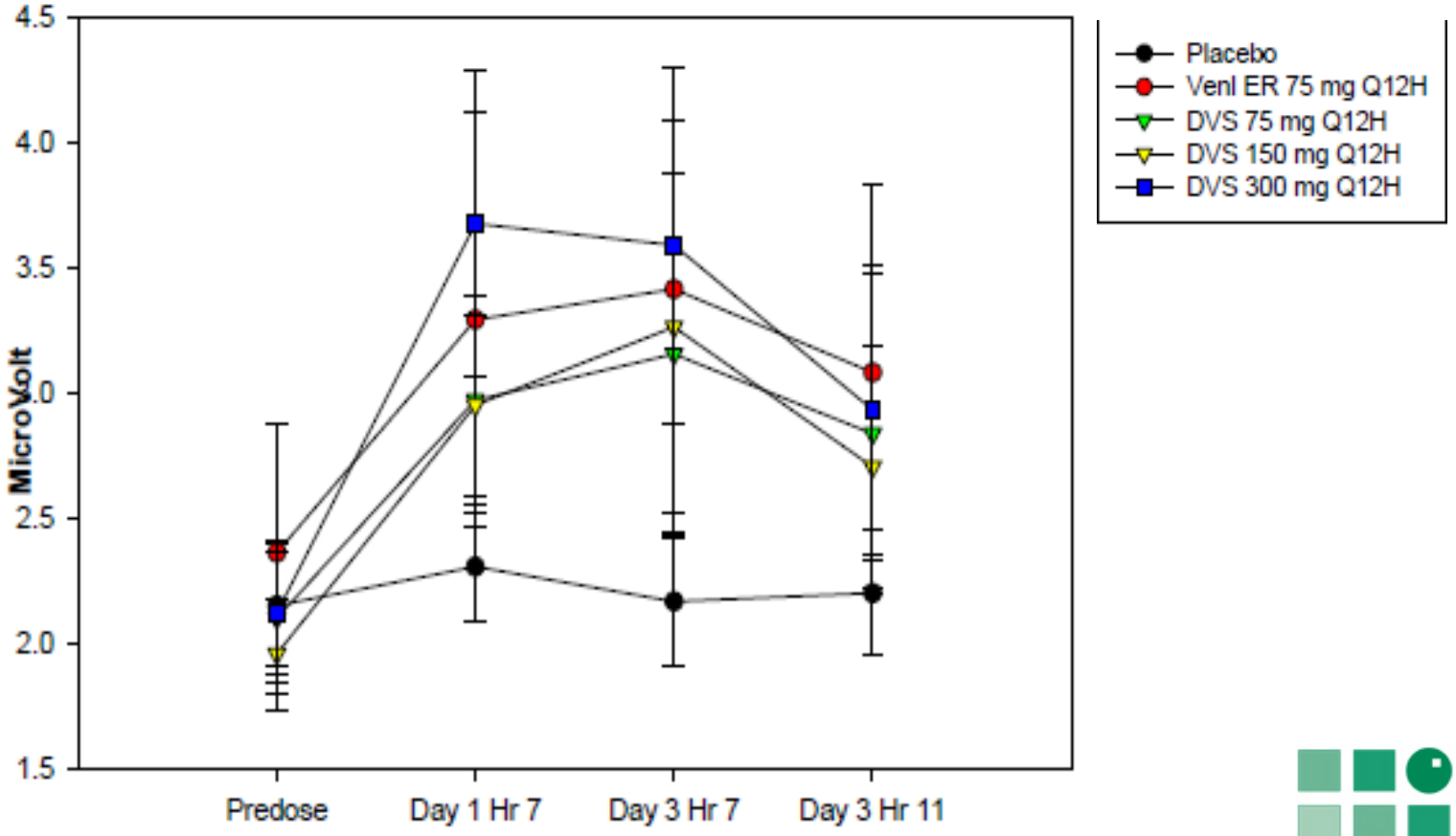
Polysomnography healthy humans sensitivity matrix

			Sleep Continuity	Sleep Architecture		
			Wake	REM sleep	Spindles (ST2)	Delta (SWS)
Acetylcholine	n-AchR agonist	Nicotine	▲	▼	▼	▼
	m-AchR antagonist	RS-86		▲	•	•
	m-AchR agonist	Scopolamine	•	▼	•	•
	AchE inhibitor	Donepezil	•	▲	▼	•
Norepinephrine	Alpha 1 antagonist	Prazosin	▼	▲	•	•
	Alpha 2 agonist	Clonidine (high dose)	▼	▼	▲	•
	NET inhibitor	Desipramine	▲	▼	•	•
Serotonin	5-HT1a agonist	Ipsapirone	•	▼	•	▼
	5-HT2a antagonist	APD-125	▼	•	▼	▲
	5-HT3 agonist	SR57227A	•	▼	•	•
	SERT inhibitor	Citalopram	•	▼	•	•

BIOTRIAL

qEEG after a single and multiple doses of antidepressants in 20 healthy subjects

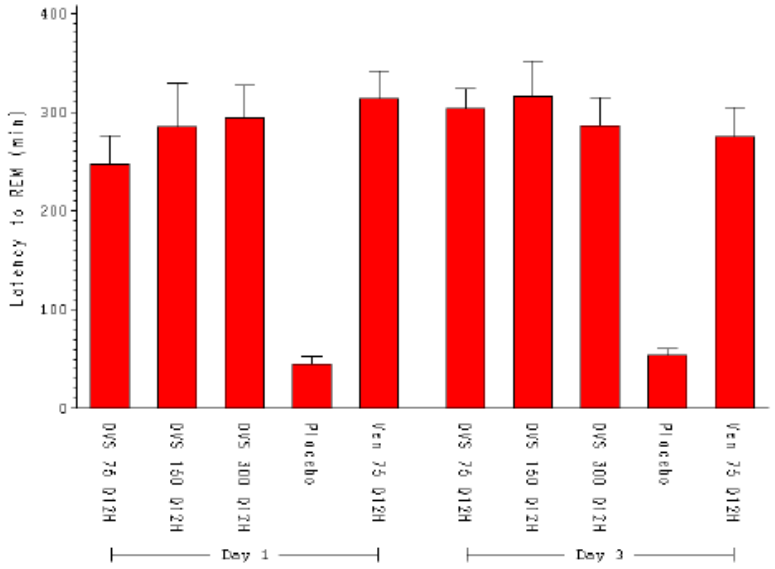
LEFT FRONTO-TEMPORAL (F3T3) BETA ABSOLUTE ENERGY



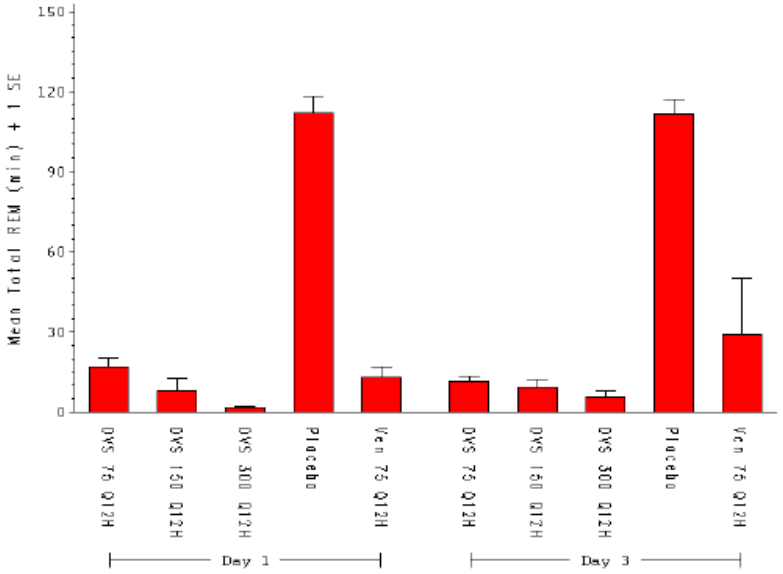
BIOTRIAL

PSG after a single and multiple doses of antidepressants in 20 healthy subjects

LATENCY TO REM SLEEP

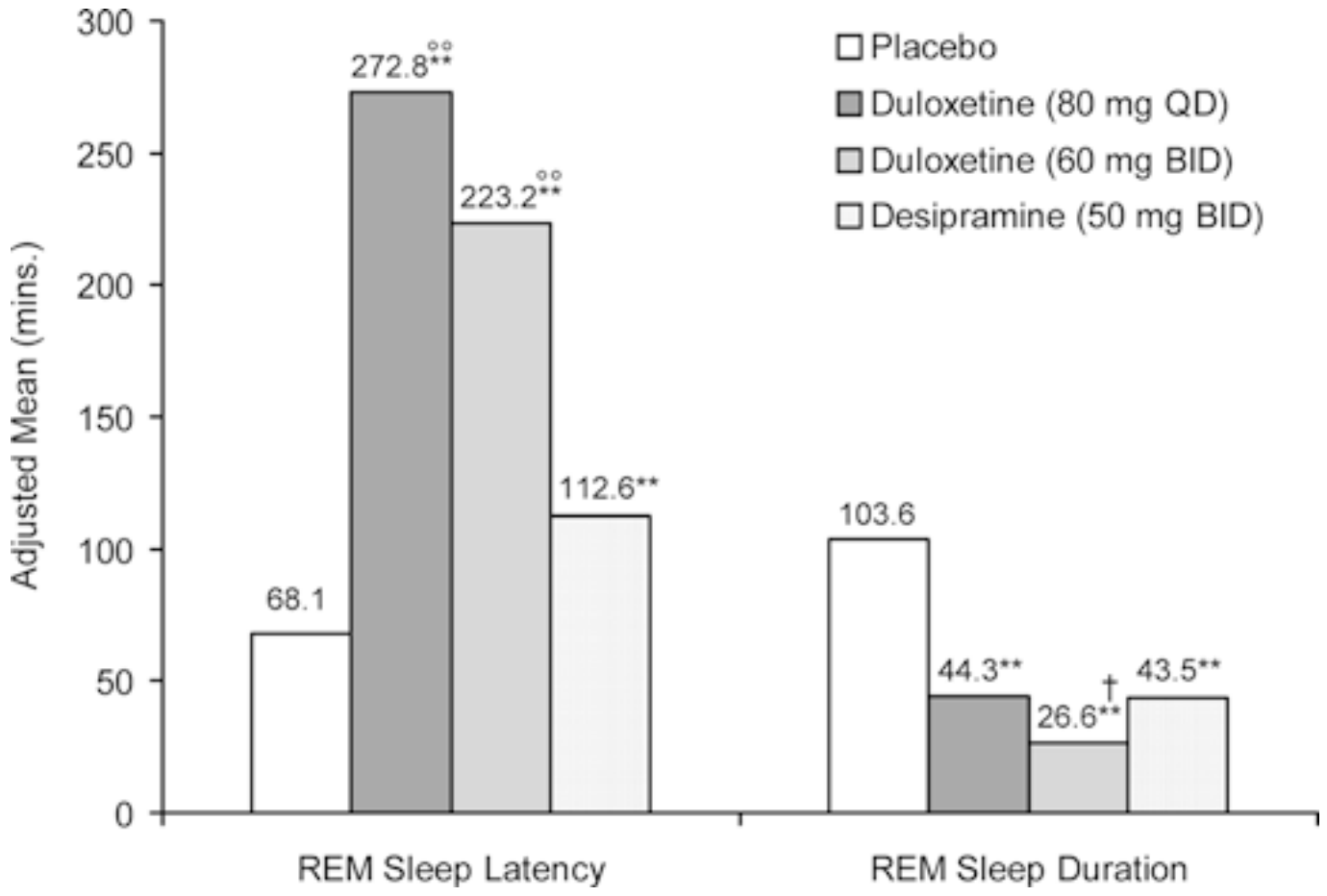


ABSOLUTE REM SLEEP DURATION



BIOTRIAL

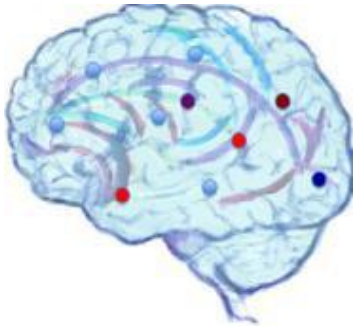
Effects of duloxetine, a SNRI versus reference desipramine on REM sleep



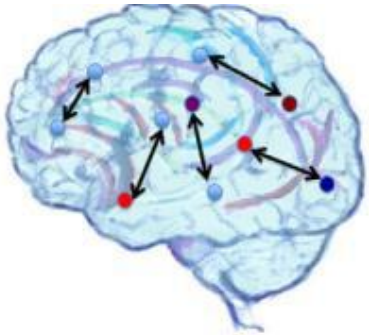
From Chalon et al. Psychopharmacology 2005

BIOTRIAL

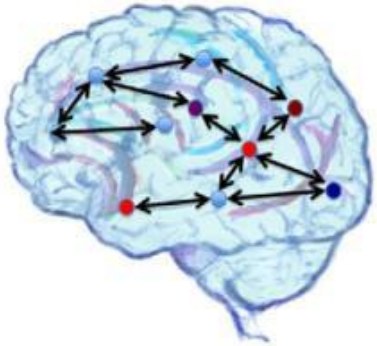
EEG analysis : current and future analysis



Local activation



Pair-wise interactions

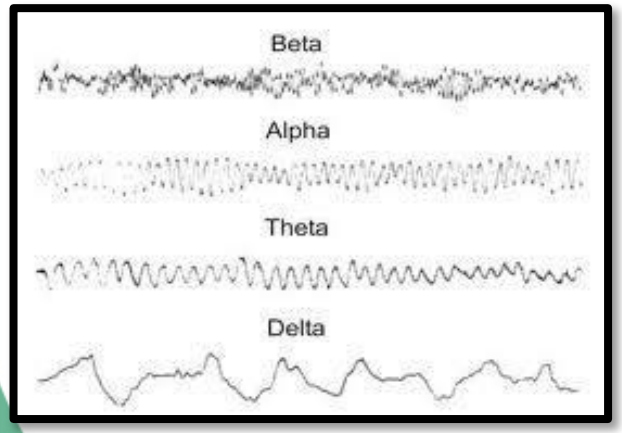


Network organization

Level 1
Basic signal analysis

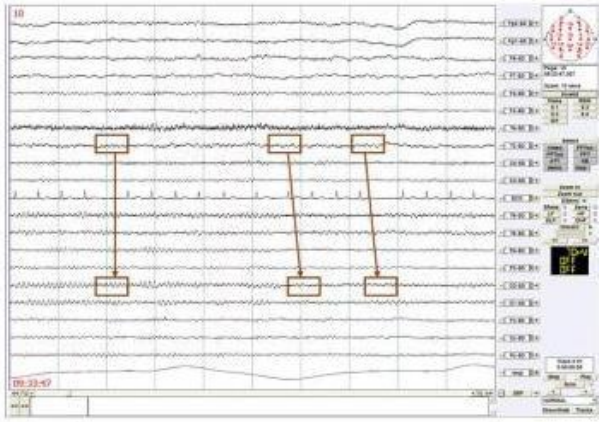
Level 2
Connectivity analysis

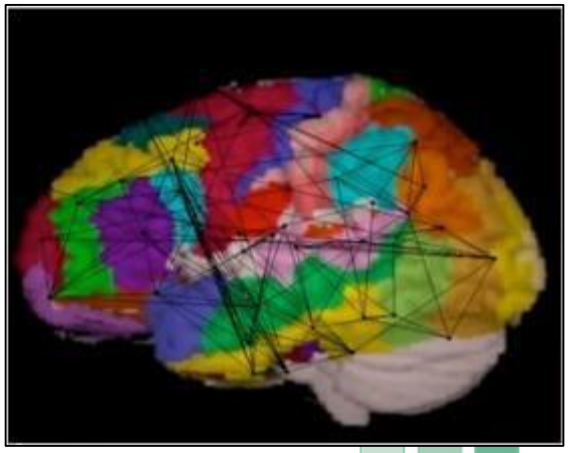
Level 3
Network analysis



Stam & van Straaten 2012

Different brain areas signal correlations ➔ functional connection





BIOTRIAL

PRISM (Psychiatric Rating using Intermediate Stratified Markers) IMI PROJECT

- European IMI aiming to unpick biological reasons underlying social withdrawal which is a common early symptom of schizophrenia (SZ), Alzheimer's disease (AD) and major depression 5MD).

- Public private collaboration involving academic units, CROs (P1vital, Biotrial) & pharmaceutical companies (Lilly, Boehringer, Janssen, Takeda, Roche, Novartis, Pfizer …)

- Objective: develop a quantitative approach to the understanding of neuropsychiatric diseases (SZ, AD, MD) relying mainly on Imaging and EEG/ERP assessments through conducting a clinical trial in 140 patients.
  4 sites.

- Back translation approach to develop preclinical tasks

PRISM

BIOTRIAL

imi innovative medicines initiative

efpia

CONCLUSION

- EEG and ERP are **useful biomarkers and translational tools** for **development of CNS compounds**
- EEG allows profiling and detecting **effects of CNS drugs in the brain in humans and animals** (Minimum Effective Dose, time-course, PK/PD, contribution of metabolites, PD interactions and synergistic effects etc).
- Portable, non invasive, reliable and cost-effective measures of **CNS functional activity**: sedation and activation for qEEG, wake-sleep stages for polysomnography and cognitive activation for ERP
- Sample size has to be carefully estimated depending on effect size of the drug (massive for BZD, NMDA antagonists, subtle in most of the cases).
- EEGs can be assessed during FIH, dedicated PD, DDI & bioequivalence/bioavailability PD studies.
- **ERP probe specific functions with specific objectives** and sometimes may be meaningless in healthy subjects (e.g. no deficit in auditory gating)
- Complementary to other methods with a higher spatial resolution such as imaging (BOLD fMRI or ASL)
- Good properties for being used to phenotype subgroup of a pathological population (PRISM) suitable for multi-center studies

Thank You for your attention

BIOTRIAL
DRUG EVALUATION AND PHARMACOLOGY RESEARCH