

The slide features a decorative background with several light blue circles of varying sizes and a thin blue horizontal line. The main title is centered and enclosed in a blue L-shaped frame on the left side.

Symposium: EEG Based Personalized Medicine

Ulrich Hegerl
Martijn Arns

In memorian Dieter Bente

- In memorian published in 1984
- A senior and founding member of IPEG
- One of his main research themes was 'EEG Vigilance' which he conceptualized in 1964

The most proper way of keeping *Bente* in kind remembrance as well as keeping his way of thinking and his scientific activity alive may well be to accept this challenge by critically re-evaluating it.

H. Künkel, Hannover

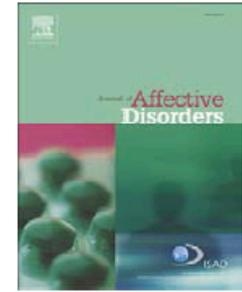
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- Vigilance Regulation and response to psychostimulants in affective disorders - Ulrich Hegerl
 - EEG-based assessment of vigilance regulation in major depression and cancer-related fatigue - Sebastian Olbrich
 - The change of prefrontal QEEG cordance as a predictor of response to antidepressant treatment - Martin Brunovsky
 - An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study - Martijn Arns
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Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad



Research report

An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study

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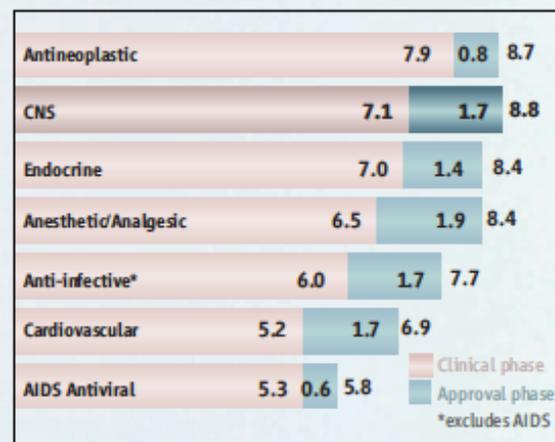
www.brainclinics.com

Is Pharma Running Out of Brainy Ideas?

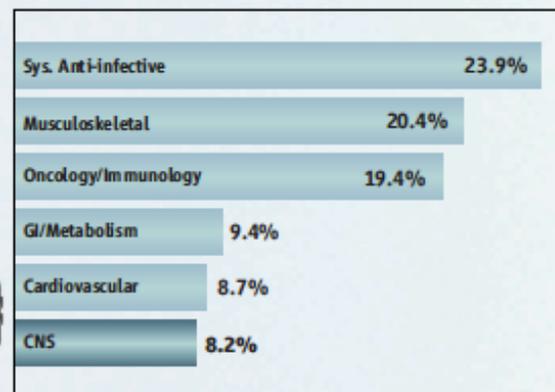
Recent cutbacks raise concerns about the future of drug development for nervous system disorders



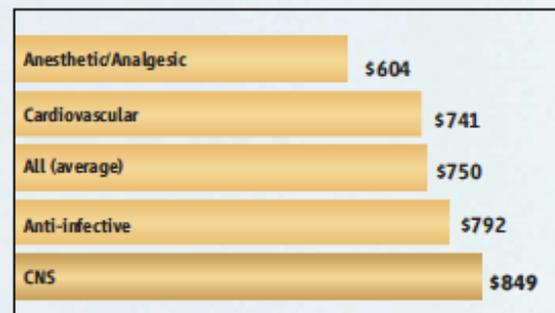
Reasons to Be Nervous



Clinical development and approval time (years)



Clinical approval success rate



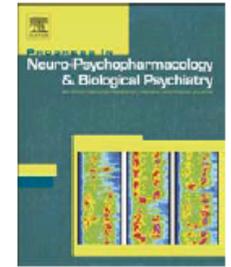
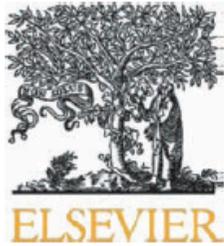
Capitalized clinical development costs (in millions)

Personalized Medicine in Psychiatry

- Efficacy of current pharmaceutical treatments seem maximal (AD 40%; Ritalin 70-90%)
 - Efficacy of newer drugs (i.e. TCA vs. SSRI) are not dramatically improved, mainly improved side effect profile
 - Limited long-term effects of stimulant medication (MTA trial)
 - Several pharmaceutical companies (GSK, AstraZenea) will no longer develop psychiatric medications (Miller, 2010)
 - Current DSM-based treatment approach not valid!
 - Personalized medicine: Right treatment, for the right person at the right time as opposed to 'Blockbuster' approach
 - Assumes heterogeneity rather than homogeneity within a psychiatric disorder!
 - No EBM Personalized Medicine application in psychiatry yet...
-

Thinking from the Neurobiological Phenotype (i.e. EEG) rather than from behavior

- EEG Vigilance: Labile or Rigid vigilance regulation
 - Relation to behavior but not a linear correlation
 - EEG Phenotypes:
 - I.e. Low Voltage EEG genetically linked to HTR3B, CRH-BP, GABA-A receptor genes (Enoch group).
 - Alpha peak frequency linked to COMT gene (Bodenmann et al., 2009)
 - Integrative approach
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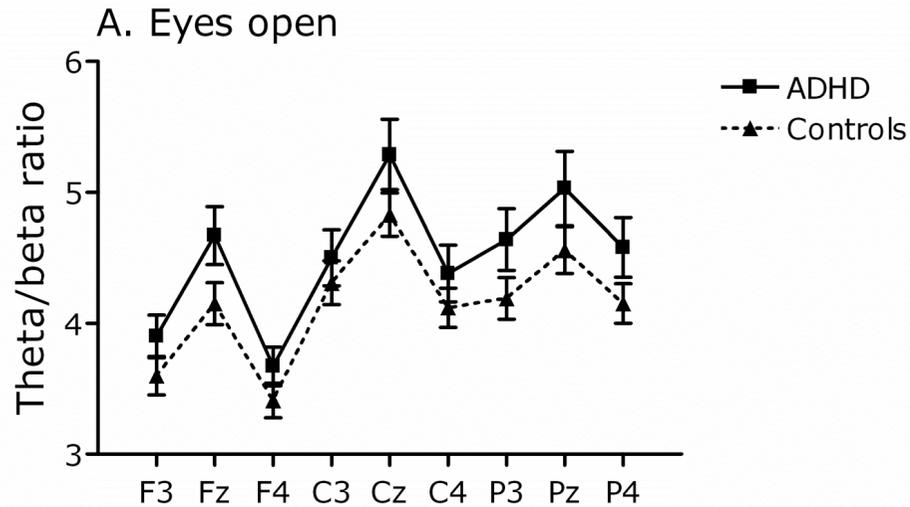


The increase in theta/beta ratio on resting-state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency

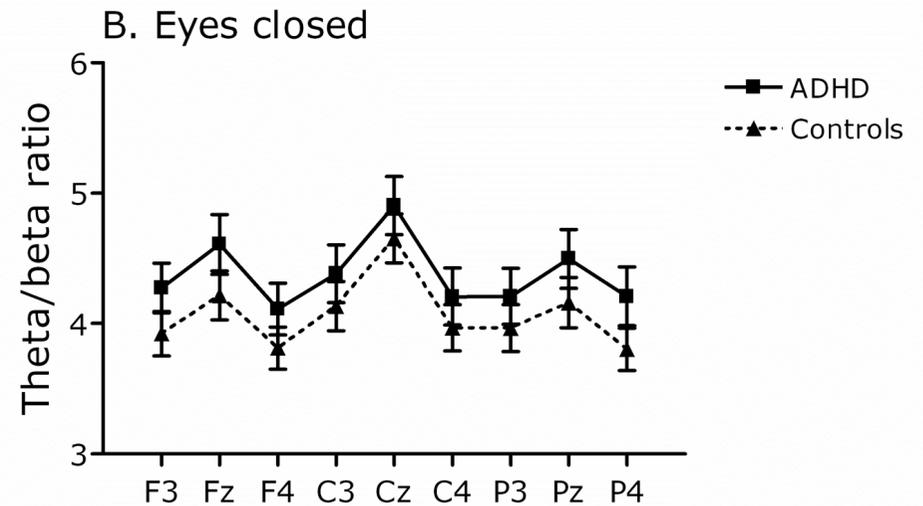
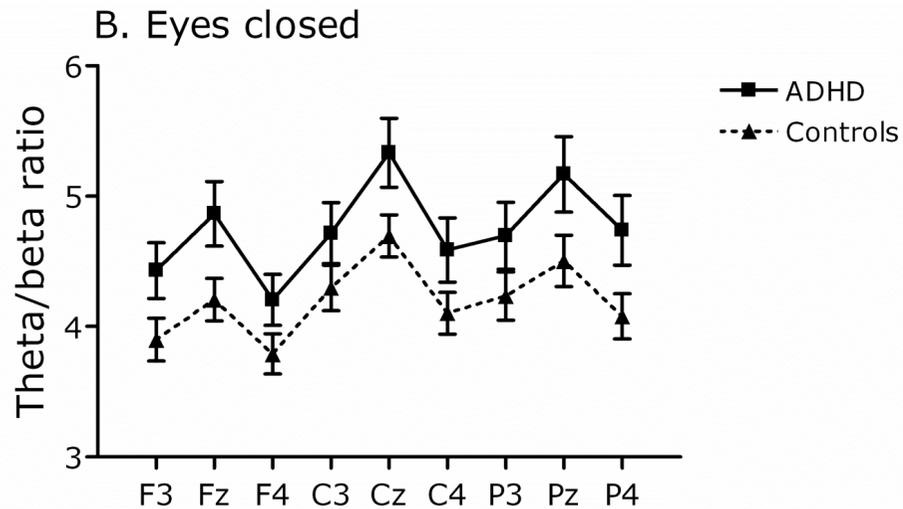
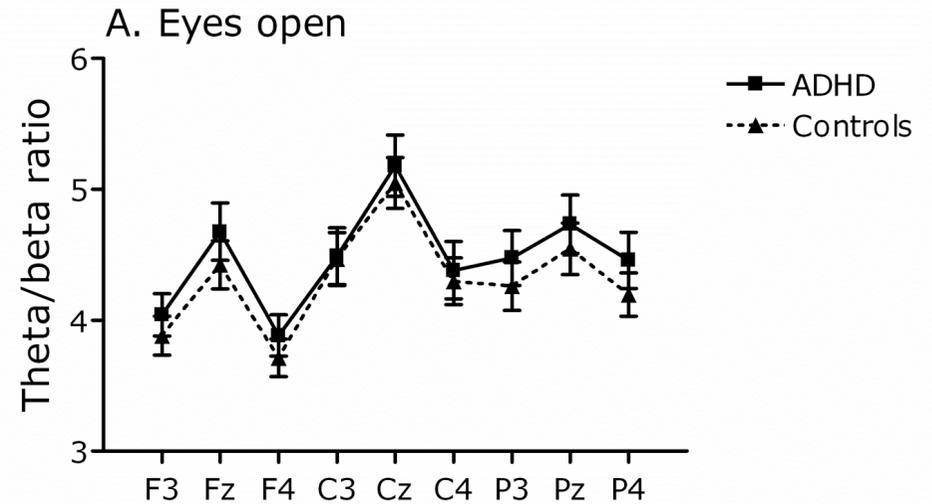
Marieke M. Lansbergen ^{a,*}, Martijn Arns ^{b,c}, Martine van Dongen-Boomsma ^{a,d},
Desirée Spronk ^{a,b}, Jan K. Buitelaar ^{d,e}

- APF matures with age and can vary between 5-14 Hz and fixed frequency bands do not accommodate deviating APF's (Klimesch, 1999)
 - Theta/Beta ratio calculated using:
 - Fixed Frequency bands (4-7.5 Hz / 12.5-25 Hz)
 - 'Individual' frequency bands (Based on IBIW method from Doppelmayr et al., 1998).
 - ADHD and control group matched on age
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Theta/Beta ratio using Fixed
frequency bands: Significant effect
 $p=.038$



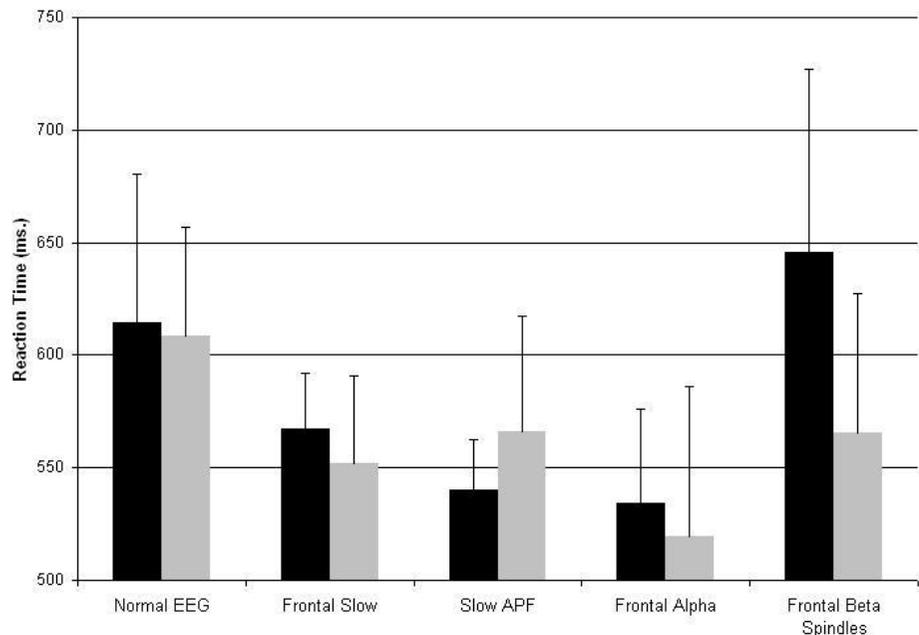
Theta/Beta ratio using Individual
frequency bands: NO significant
effect



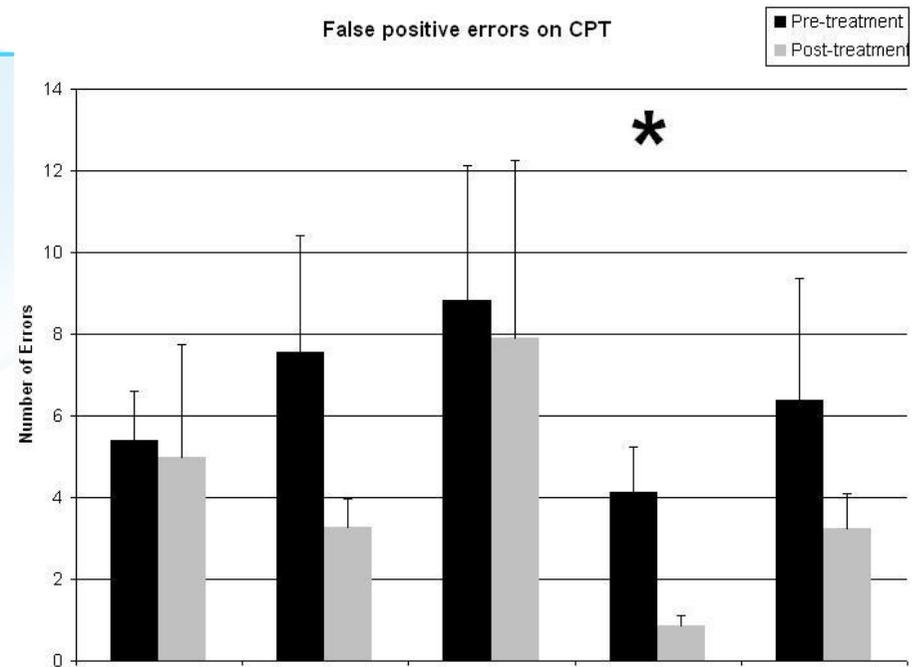
Does EEG predict treatment outcome?

- 'Frontal slow': Decreased false negative errors: Inattention
- 'Frontal alpha': decreased false positive errors: Impulsivity.

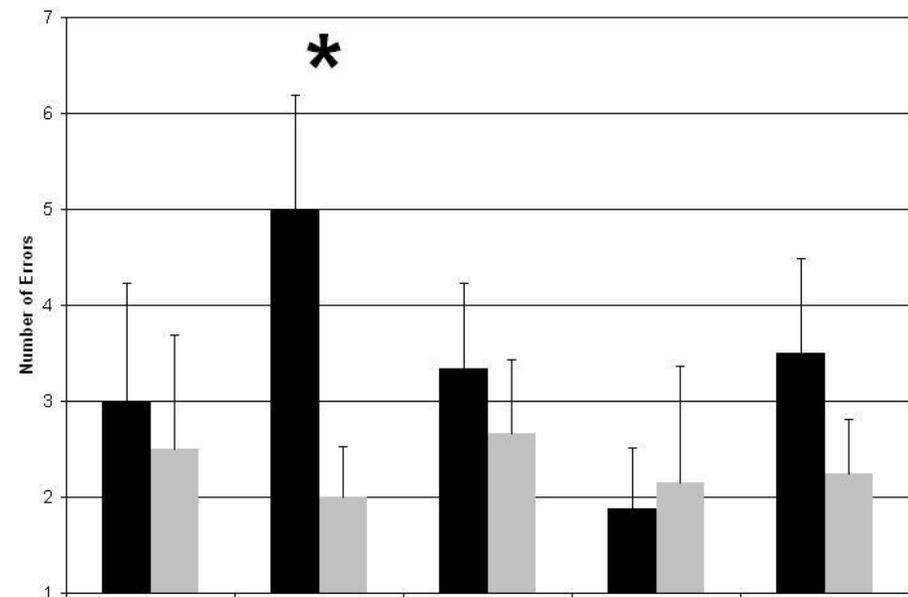
Reaction time during CPT



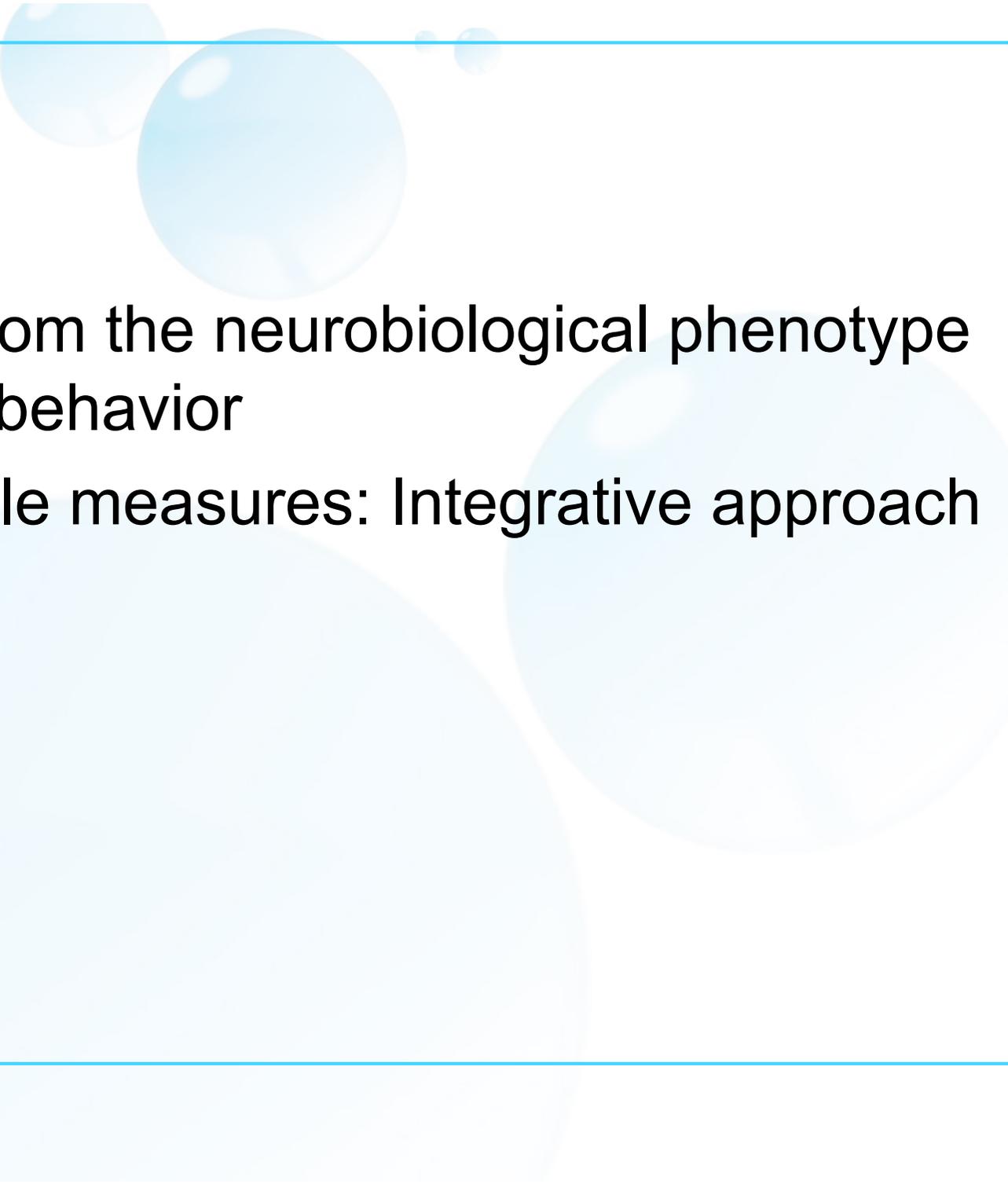
False positive errors on CPT



False negative errors on CPT



Arns, M., Gunkelman, J., Breteler, M., & Spronk, D. (2008). EEG phenotypes predict treatment outcome to stimulants in children with ADHD. *Journal of Integrative Neuroscience*, 7(3), 421-38.

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- The slide features a decorative design with several light blue circles of varying sizes and a thin blue horizontal line at the top. The circles are positioned in the upper and lower portions of the slide, with some overlapping. The text is centered in the middle of the slide.
- Thinking from the neurobiological phenotype instead of behavior
 - Use multiple measures: Integrative approach
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Treatment prediction in Depression

- First report of prognostic use by Roth et al. (1957)
 - Barbiturate induced changes (delta increase) predicted long term outcome to ECT (3-6 mo.)
- Other well investigated Biomarkers in depression:
 - Neurophysiology:
 - LDAEP: Hegerl, Gallinat & Juckel, 2001
 - EEG Cordance: BRITE-MD trial -> Brunovsky
 - EEG Vigilance: -> Hegerl
 - EEG Alpha Asymmetry: Bruder et al. 2001
 - Neuropsychology:
 - Improved Neuropsychological performance
 - Genetics:
 - BDNF, COMT, 5-HT genes, results inconsistent.
- All studies using single measure, no integrative studies

Methodology

- Sample of 31 patients, 25 had complete data
- Open-label non-randomized
- Subject prescribed with an SSRI/SNRI/TCA

Demographics and clinical characteristics.

Variable	Mean (SD)
Age	42.8 (14.2)
Male/Female	7/18
Years of education	14.2 (3.1)
HAM-D-17 baseline	20.2
HAM-D-17 week 8	11.2
SSRI/SNRI/TCA	14/8/2*

Analysed data

- QEEG: Eyes Open / Closed EEG (Delta, Theta, Alpha, Beta; Fz, Cz, Pz)
 - ERP: Auditory oddball, Continuous Performance Test (n-back): Fz, Cz, Pz
 - DNA: Cheek swab sample:
 - BDNF (Brain Derived Neurotrophic Factor)
 - COMT (Catechol- O-Methyl Transferase)
 - Grouping of homozygote genotype with lowest prevalence (COMT V/V; VM vs. M/M; BDNF: M/M; V/M vs. V/V)
 - Multiple regression models with absolute change in HAM-D (wk. 8) as dependent variable.
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Cognitive measures

- Total memory score: $R^2 = .263$

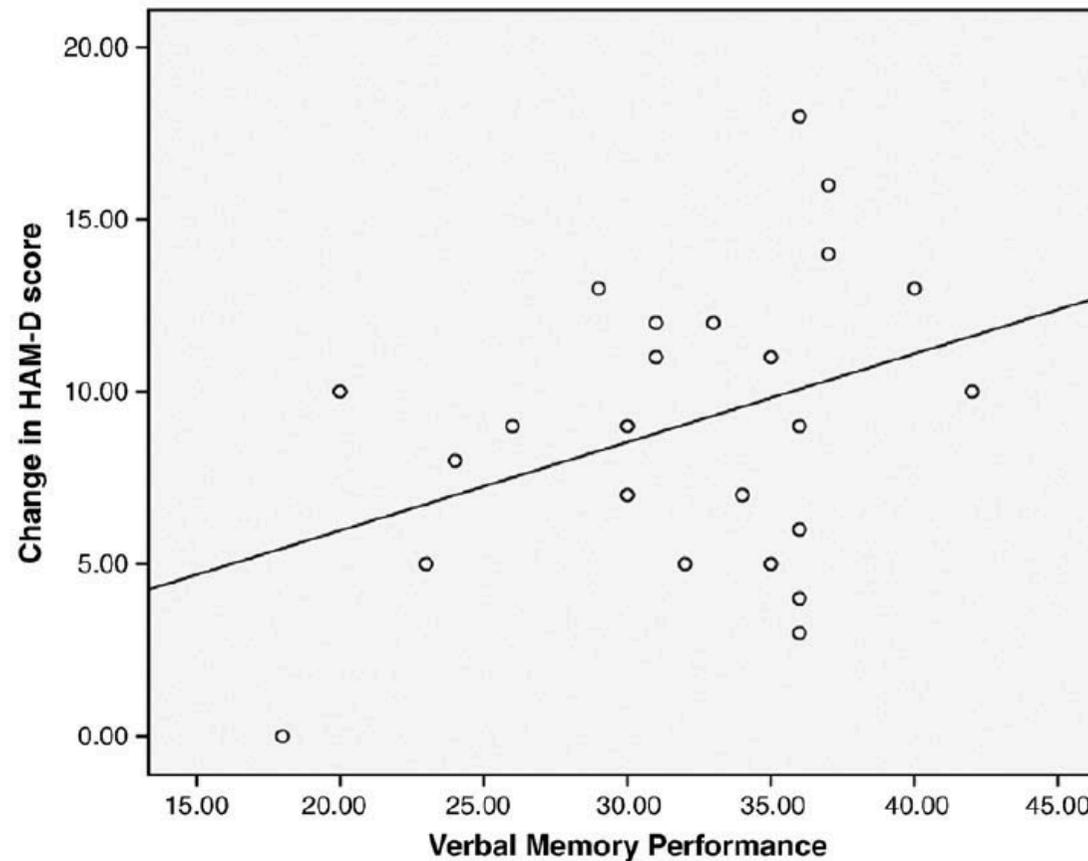


Fig. 1. Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and verbal memory performance.

ERP measures

- Oddball N100 @ Pz amplitude: $R^2 = .369$

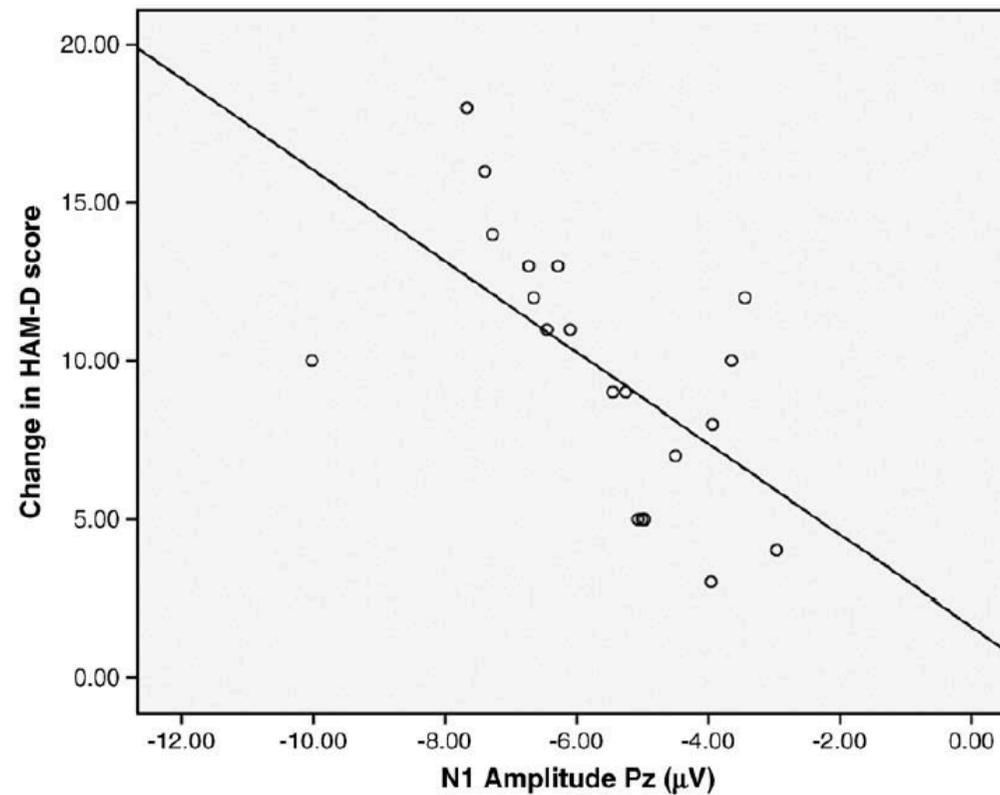


Fig. 2. Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and pretreatment N1 amplitude as measured in an Auditory Oddball task.

EEG Measures

- Theta power @ Fz: $R^2 = .236$

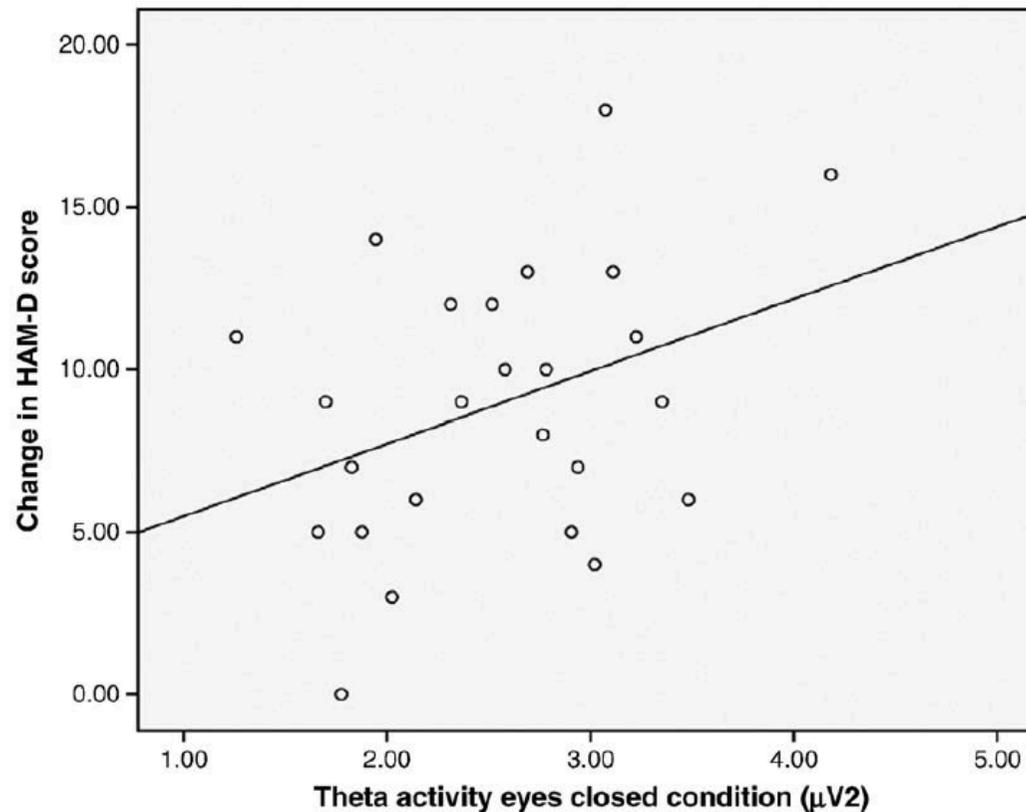


Fig. 3. Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and pretreatment absolute Theta power measure during the rest EEG eyes closed task.

Genetics

- COMT: $R^2 = .318$:
- COMT Met/Met positive predictor for treatment outcome.

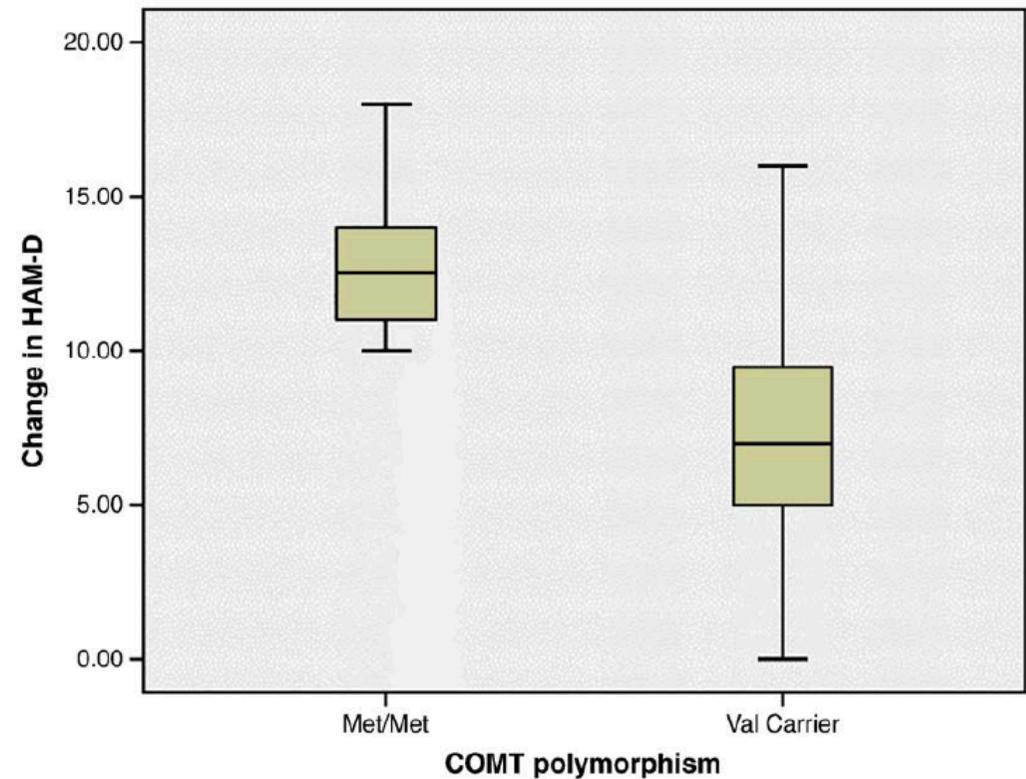


Fig. 4. Individual COMT genetic variants against change in HAM-D score.

Integrative model

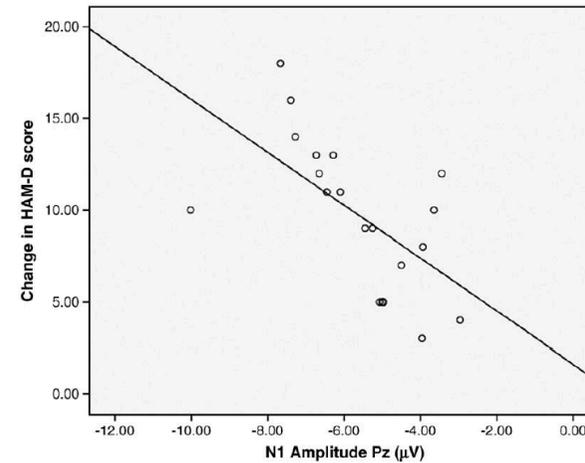
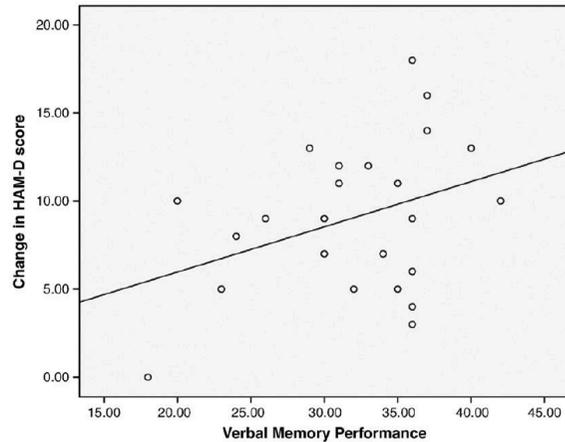


Table 2
Model parameters integrative model.

Model		<i>B</i>	SE	<i>t</i> -statistic	<i>p</i>
Step 2	Baseline HAM-D	-0.179	.181	-0.988	.334
	N1 amplitude at Pz	-1.581	.381	-4.145	.001
	Verbal memory performance	0.300	.0100	2.994	.007

$R^2 = .602.$

Conclusions

- Integrative model explained most of the variance.
 - Different predictors have different predictive validity (overlap between N100 ampl and verbal memory was only 3%!)
 - No added value of genetics and EEG in this model.
 - Baseline HAM-D was a covariate but non-significant.
 - Increased Frontal theta marker:
 - Decreased frontal theta? (Suffin & Emory, 2005; Knott et al., 1996)
 - Increased theta in anterior cingulate? (LORETA studies: Pizzagalli et al., 2001 - AD; Narushima et al., 2010 - rTMS)
 - Predictive validity of main class (AD) or subclass (SSRI, SNRI, TCA)?
 - Small sample size: Pilot study
-

iSPOT-A and iSPOT-D

- Replication in a larger sample:
 - iSPOT trial: international Study for Optimized Treatment response in Depression and ADHD
 - Largest international trial on Personalized Medicine in Depression (N=2000) and ADHD (N=500) using medication
-

Thank you for your attention!

Acknowledgement:
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Brain Resource Company
