Suore Ospedaliere

FORIPSI
FONDAZIONE INTERNAZIONALE PER IL SOSTEGNO DELLA RICERCA IN PSICHIATRIA

Personalized Psychiatry & Panic Disorder: from Genetics to Endophenotypes

presented by.

Giampaolo Perna, MD, PhD

WPA Madrid, 16th September 2014

UHealth UNIVERSITY OF MIAMI HEALTH SYSTEM | UNIVERSITY OF MIAMI MILLER SCHOOL of MEDICINE

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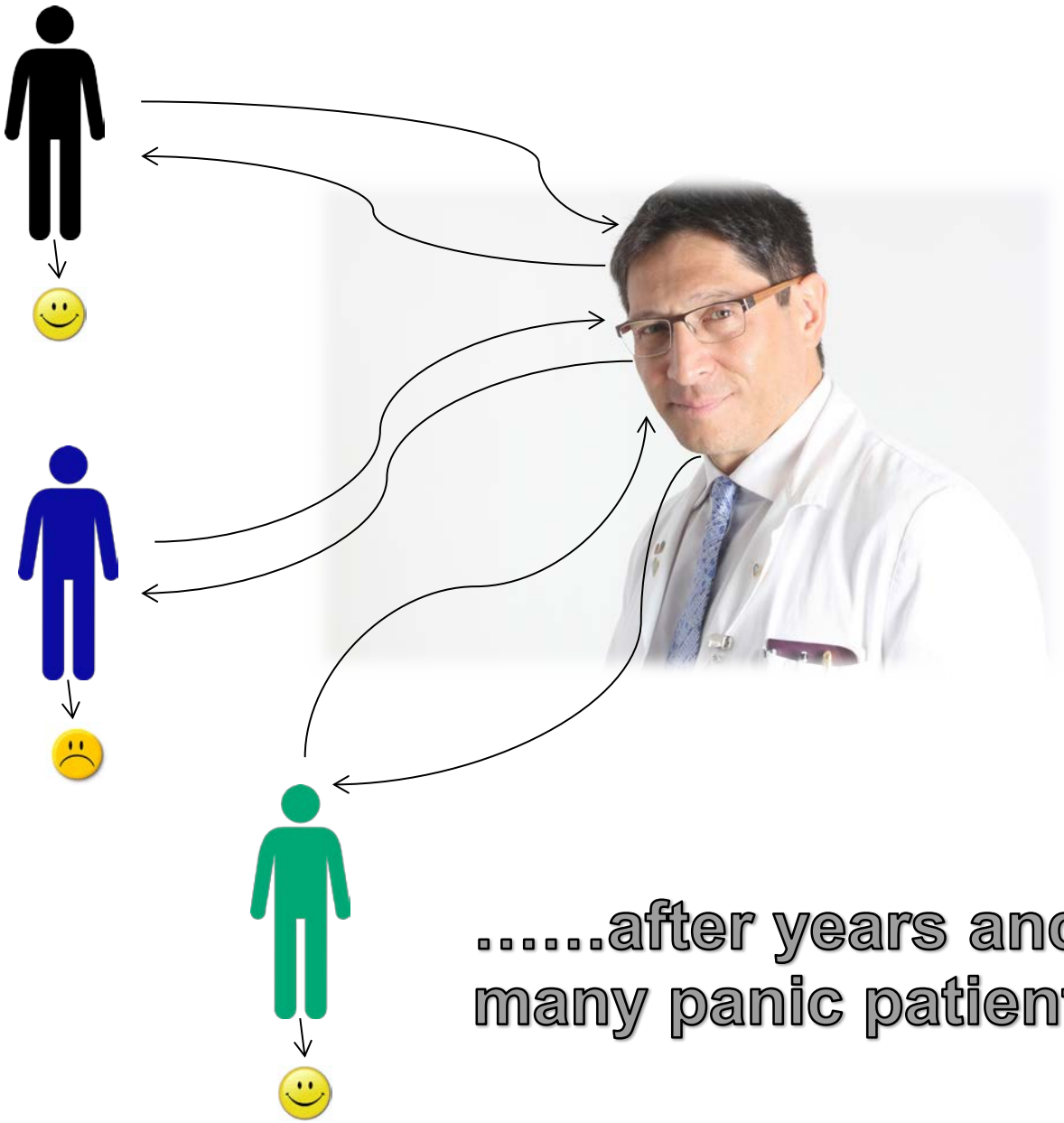
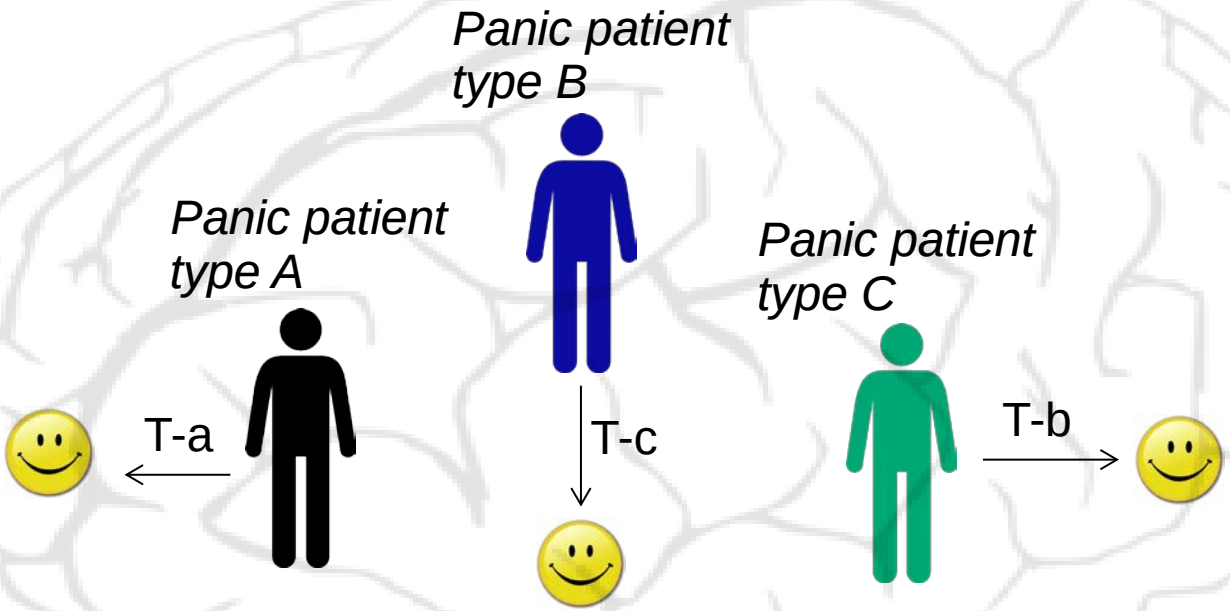
Personalized Psychiatry:

is it really something new?



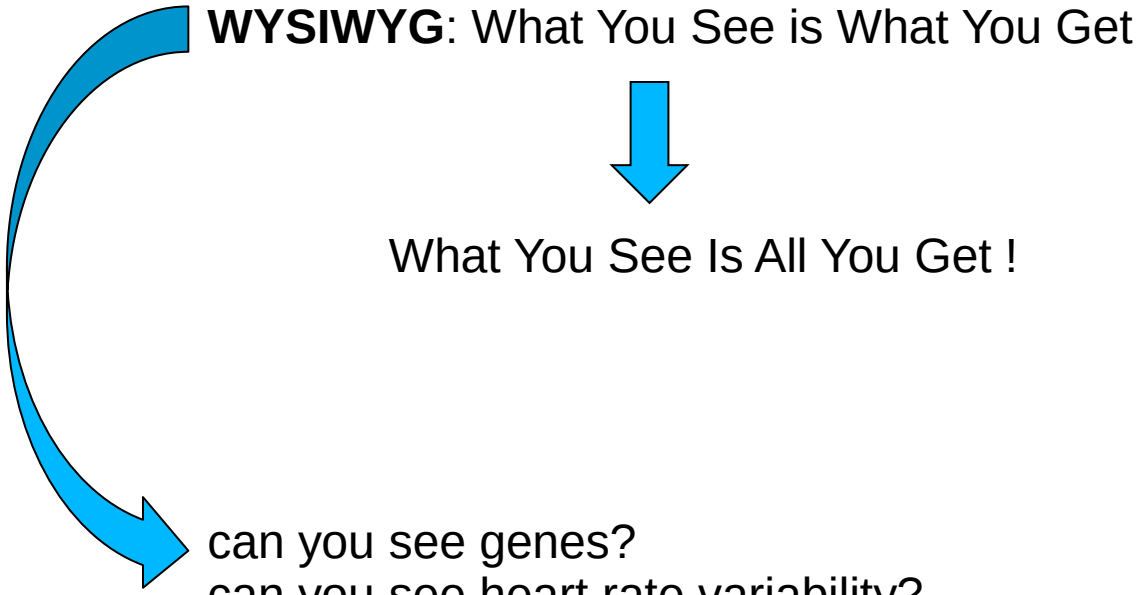
……after years and many, many panic patients


Panic patient
type B
Panic patient
type A
Panic patient
type C
T-a
T-c
T-b

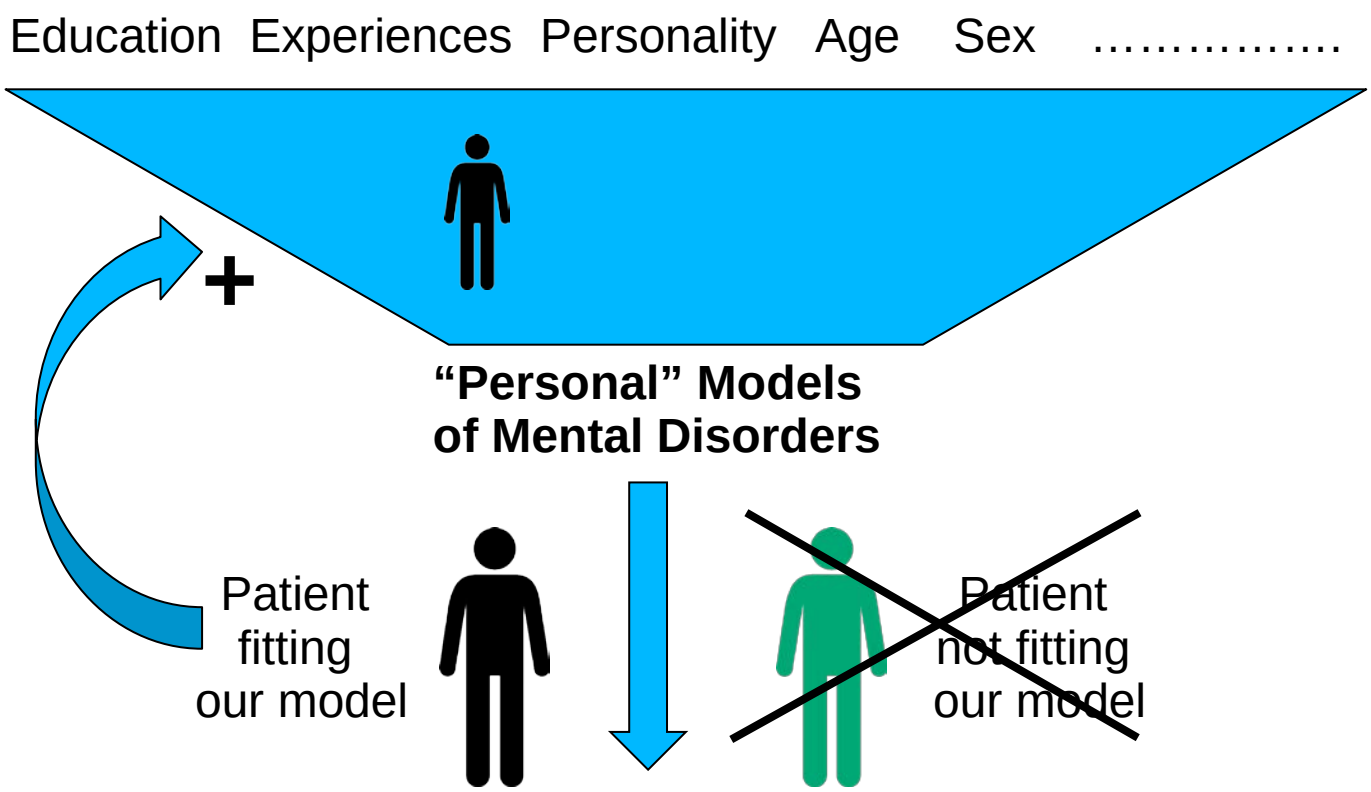
Personalized Psychiatrist:

is this enough?

Personalized Psychiatrist approach: Biases…….



Personalized Psychiatrist approach: Biases…….



We See What We Want to See

Personalized Psychiatry as a Science will help us to:

To move from the science of “mean ideal patient” to the science of “real life patient”

To become better Personalized Psychiatrists:

- overcoming our personal biases
- including “hidden” information in our thinking
- opening our mind to ideas of others

……after 25 years of more than 5’000 panic patients

Panic Perna Personalized Psychiatry (P4)

1. Respiratory, Cardiac, Vestibular Patterns are those specific for Perna's True Panic Patients

2. Cardiorespiratory patients respond better to paroxetine and clomipramine

3. Patients with otovestibular symptoms respond better to sertraline

4. Clomipramine works on dyspnea panic patients

5. Fluovamine does not work in panic patients

6. Cardiorespiratory patients respond quicker than depersonalization patients

7. Paroxetine & SSRIs are protective on cardiovascular system

8. CO2 hypersensitivity is an endophenotype of true panic patients

9. ……

10……

Personalized Psychiatry & Panic Disorder:

a Systematic Review of Predictors of Efficacy of Antipanic treatments

Key words in PubMed database (up to 15 August)

("panic disorder"[TIAB] AND ("predict*" OR (("treatment*" OR "therapy" OR "therapies" OR "pharmacotherapy" OR "psychotherapy") AND "response") OR "pharmacogen*" OR "longitudinal" OR "artificial neural network" OR "artificial neural networks" OR "support vector machine" OR "support vector machines"

References obtained: 1167

References selected: 171

Not predictors of response to treatment:

1. Agoraphobia (both drugs and CBT)(9/9 studies)
2. Diagnosis of Depression (both drugs and CBT (5/6 studies)
3. Duration of illness (both drugs and CBT) (11/11 studies)
4. Gender (both drugs and CBT) (19/22 studies)
5. Age (both drugs and CBT) (16/19 studies)

Discordant data:

1. Panic Severity
2. Anxiety Severity (discordant for drugs, negative for CBT)
3. Depressive symptomatology
4. Respiratory subtype

Predictors of response to treatment:

1. Blood levels of Antipanic drugs
   (9/10 studies)

1. Early response to treatment (both drugs and CBT)
   (5/5 studies)

1. Personality Disorders comorbidity (both drugs and CBT
   (8/9 studies)

Personalized Psychiatry & Panic Disorder:

Genetics

Neuropsychopharmacology (2005) 30, 2230–2235

www.neuropsychopharmacology.org

Antipanic Efficacy of Paroxetine and Polymorphism within the Promoter of the Serotonin Transporter Gene

Giampaolo Perna*[,1], Elisa Favaron[1], Daniela Di Bella[1], Riccardo Bussi[1] and Laura Bellodi[1]

[1]*Anxiety Disorders Clinical and Research Unit, Istituto Scientifico H.S. Raffaele, Vita-Salute University, Milan, Italy*

Table 2 Treatment Outcome and 5-HTTLPR Variants in Female Patients with PD

	l/l	l/s	s/s
Δ%PASS*	82.3 ± 34.3	79.5 ± 21.9	59.1 ± 31.6
Good Responders*	6/8 (75%)	17/31 (55%)	2/12 (17%)
No panic attacks at week 12*	6/7 (86%)	16/30 (53%)	1/9 (11%)
No anticipatory anxiety at week 12	5/8 (63%)	12/29 (41%)	2/12 (17%)
No agoraphobia at week 12	5/6 (83%)	13/22 (59%)	7/11 (64%)

*$p < 0.05$.

Table 3 Treatment Outcome and 5-HTTLPR Variants in Male Patients with PD

	l/l	l/s	s/s
Δ%PASS	83.5 ± 30.8	80.5 ± 20.3	64.7 ± 28.0
Good responders	9/11 (82%)	12/17 (71%)	7/11 (64%)
No panic attacks at week 12	10/11 (91%)	11/16 (69%)	7/10 (70%)
No anticipatory anxiety at week 12	5/10 (50%)	6/16 (37%)	2/11 (18%)
No agoraphobia at week 12	7/8 (87%)	10/15 (67%)	5/10 (50%)

Eur J Clin Pharmacol (2011) 67:1213–1221
DOI 10.1007/s00228-011-1073-9

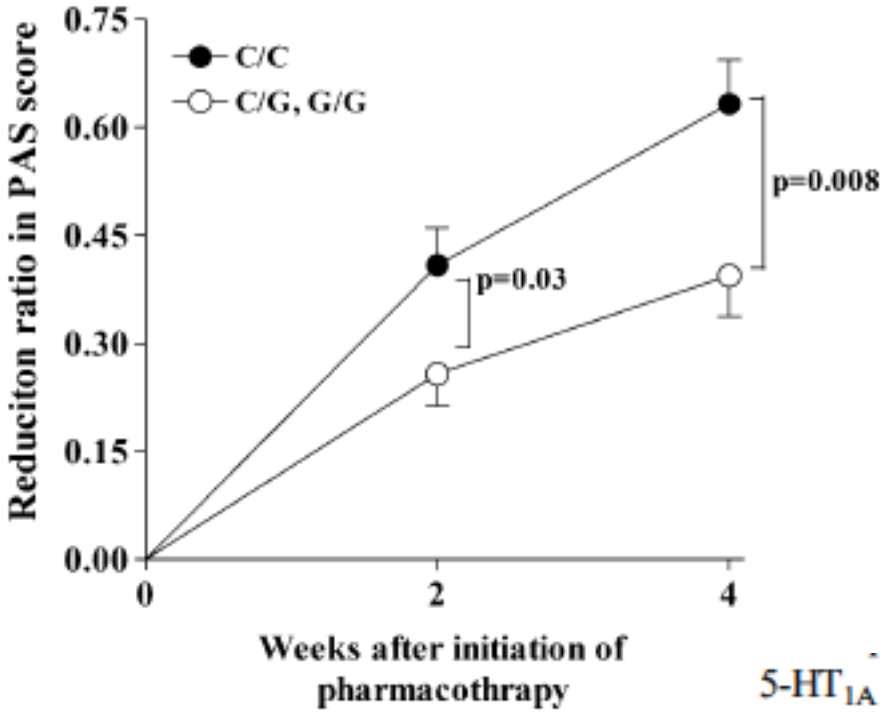
PHARMACOGENETICS

Determinants of pharmacodynamic trajectory of the therapeutic response to paroxetine in Japanese patients with panic disorder

Shin Ishiguro · Takashi Watanabe · Mikito Ueda · Yoshinori Saeki · Yuki Hayashi · Kazufumi Akiyama · Atsushi Saito · Kazuko Kato · Yoshimasa Inoue · Kazutaka Shimoda

Table 3 Results of the stepwise multiple regression analysis after 2 weeks of treatment

Independent variable	*p* value
Plasma concentration of paroxetine	0.001
5-HTTLPR genotype	0.001
$5HT_{1A}$ -1019C/G genotype	0.004



5-HT_{1A} gene promoter polymorphism.

Available online at www.sciencedirect.com
ScienceDirect
Progress in Neuro-Psychopharmacology & Biological Psychiatry 30 (2006) 1413–1418
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Tryptophan hydroxylase and serotonin transporter gene polymorphism does not affect the diagnosis, clinical features and treatment outcome of panic disorder in the Korean population

Won Kim [a], Young Hee Choi [b], Kyung-Sik Yoon [c], Dae-Yeon Cho [d], Chi-Un Pae [e], Jong-Min Woo [a,*]

[a] *Department of Psychiatry and Stress Research Institute, Seoul Paik Hospital, Inje University, Seoul, Republic of Korea*

Journal of Affective Disorders 123 (2010) 308–311

Contents lists available at ScienceDirect

Journal of Affective Disorders

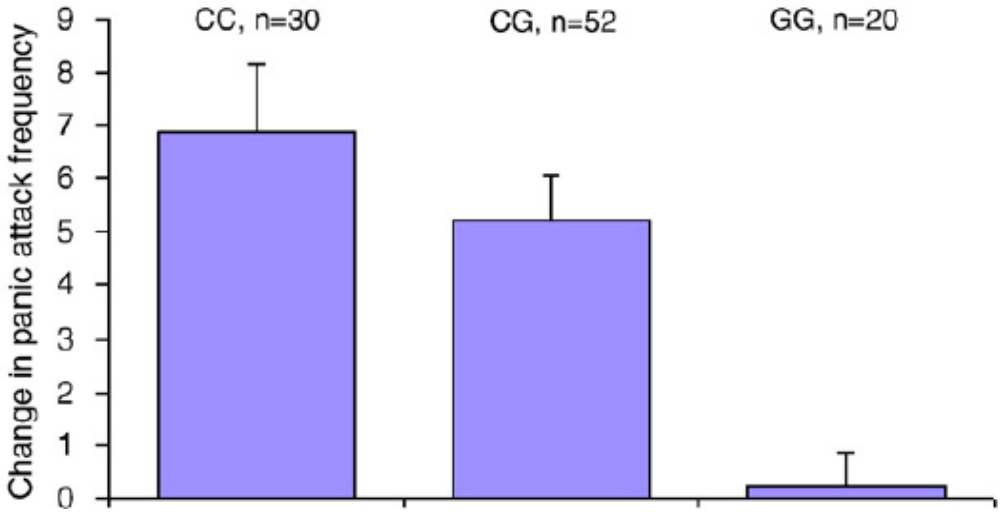
journal homepage: www.elsevier.com/locate/jad

Preliminary communication

Early response to selective serotonin reuptake inhibitors in panic disorder is associated with a functional 5-HT1A receptor gene polymorphism

Olga O. Yevtushenko [a,b,*], Mykhaylo M. Oros [c], Gavin P. Reynolds [b]

[a] Department of Neuropharmacology, Institute of Pharmacology and Toxicology AMS Ukraine, Eugene Potie str., 14, Kyiv, 03057, Ukraine
[b] Department of Psychiatry, Queen's University Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, U.K.
[c] Clinic "Vodolij", Pachovs'kogo str., 14, Khust, 90400 Ukraine



Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Psychiatric Research 38 (2004) 365–370
JOURNAL OF PSYCHIATRIC RESEARCH
www.elsevier.com/locate/jpsychires

The association between panic disorder and the L/L genotype of catechol-*O*-methyltransferase☆

Jong-Min Woo[a], Kyung-Sik Yoon[b], Young-Hee Choi[a], Kang-Sub Oh[c], Young-Sik Lee[d], Bum-Hee Yu[e,*]

[a] *Department of Neuropsychiatry, Inje University Seoul Paik Hospital, Seoul, Republic of Korea*

Table 3
Response to paroxetine treatment in panic patients according to COMT genetic polymorphism

Variable	H/H ($n = 95$)		H/L ($n = 64$)		L/L ($n = 19$)		Analysis		
	Mean	SD	Mean	SD	Mean	SD	F	df	p
CGI-SI	5.5	0.9	5.5	1.1	5.3	0.8	0.36		0.699
CGI-GI	1.9	0.9	2.2	0.9	2.8	1.1	6.73		0.002[a]

CGI-SI, pre-treatment clinical global impression scale – severity of illness; CGI-GI, clinical global impression scale – global improvement.
[a]The L/L group had a poorer treatment response than the H/H group ($p = 0.002$), but not significantly higher than L/H group ($p = 0.069$) by a post-hoc (Scheffé) test.

European Neuropsychopharmacology (2014) 24, 1222–1228

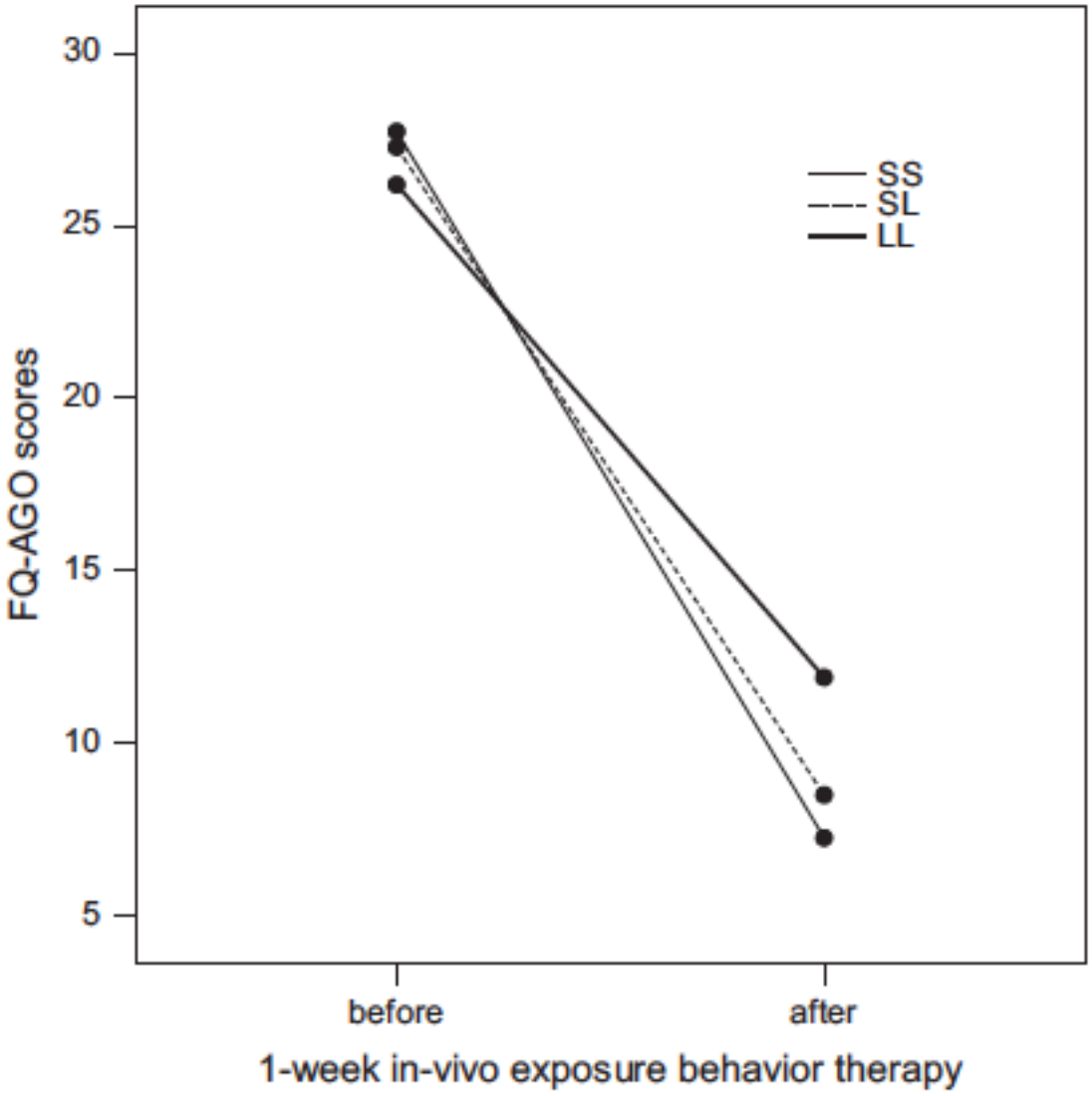
ELSEVIER

www.elsevier.com/locate/euroneuro

Therapygenetics: 5-HTTLPR genotype predicts the response to exposure therapy for agoraphobia

Inge Knuts[a,*], Gabriel Esquivel[b], Gunter Kenis[b], Thea Overbeek[b] Nicole Leibold[b], Lies Goossens[b], Koen Schruers[b]

[a]*School for Mental Health en Neuroscience, Maastricht University and Mondriaan, Vijverdalseweg 1, gebouw Concorde, 6226 NB Maastricht, The Netherlands*
[b]*School for Mental Health en Neuroscience, Maastricht University,Maastricht, The Netherlands*


30
25
20
15
10
5
FQ-AGO scores
SS
SL
LL
before
after
1-week in-vivo exposure behavior therapy

Lonsdorf et al. BMC Psychiatry 2010, 10:99
http://www.biomedcentral.com/1471-244X/10/99

BMC Psychiatry

RESEARCH ARTICLE Open Access

The COMTval158met polymorphism is associated with symptom relief during exposure-based cognitive-behavioral treatment in panic disorder

Tina B Lonsdorf[1,3,4,5,7*], Christian Rück[2], Jan Bergström[2], Gerhard Andersson[2,6], Arne Öhman[1,4,5], Nils Lindefors[2], Martin Schalling[3]

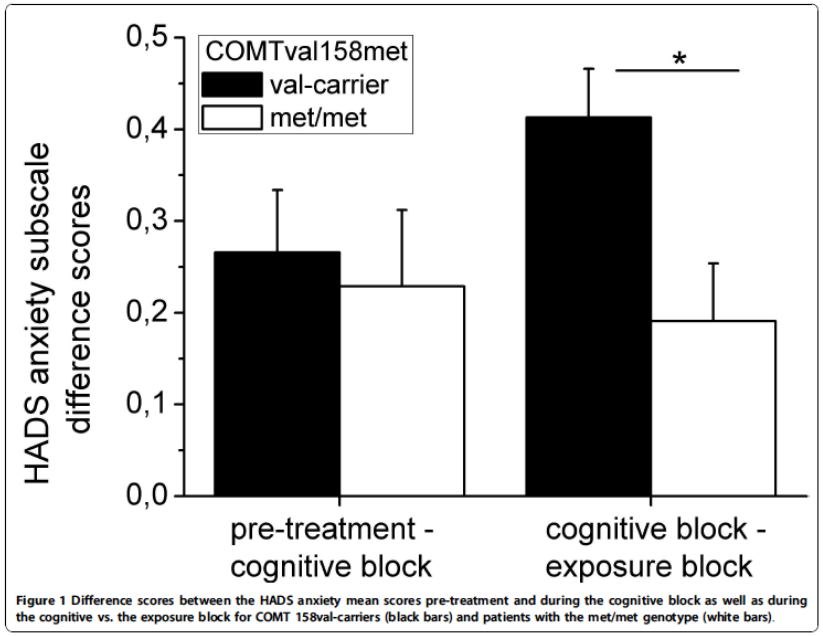


Figure 1 Difference scores between the HADS anxiety mean scores pre-treatment and during the cognitive block as well as during the cognitive vs. the exposure block for COMT 158val-carriers (black bars) and patients with the met/met genotype (white bars).

Molecular Psychiatry (2014) 19, 122–128

www.nature.com/mp

ORIGINAL ARTICLE

MAOA and mechanisms of panic disorder revisited: from bench to molecular psychotherapy

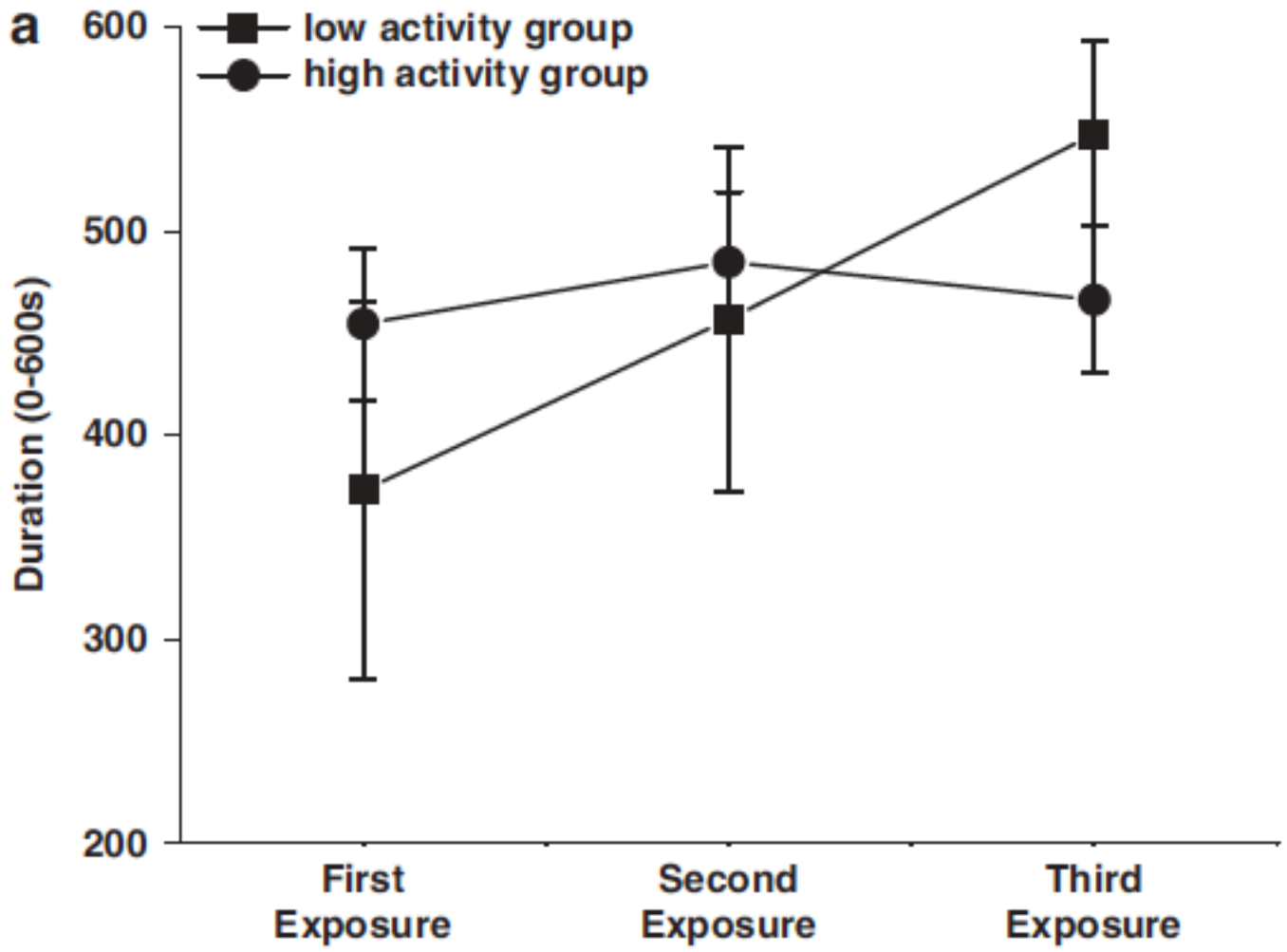
A Reif[1,14], J Richter[2,14], B Straube[3], M Höfler[4], U Lueken[4], AT Gloster[4], H Weber[1], K Domschke[1,5], L Fehm[6], A Ströhle[7], A Jansen[3], A Gerlach[8], M Pyka[3], I Reinhardt[9], C Konrad[3,5], A Wittmann[7], B Pfleiderer[10], GW Alpers[11], P Pauli[12], T Lang[13], V Arolt[5], H-U Wittchen[4], A Hamm[2], T Kircher[3] and J Deckert[1]

Table 1. Effect of *MAOA* genotype (dichotomized in high (H) and low (L) activity as defined in the Materials and methods) on therapy response in panic disorder

		HAMA			*CGI*			*Number of panic attacks*			*MI*		
Sex/genotype group	N *(total)*	N *(responder)*	% *(responder)*	P-*value*	N *(responder)*	% *(responder)*	P-*value*	N *(responder)*	% *(responder)*	P-*value*	N *(responder)*	% *(responder)*	P-*value*
LOCF analysis, N = *232*													
Males, H	41	20	48.8		13	31.7		17	41.5		21	52.5	
Males, L	19	12	63.2	0.286	12	63.2	0.035	8	42.1	0.771	9	50.0	0.816
Females, H	152	68	44.7		74	48.7		89	58.6		65	44.8	
Females, L	20	14	70.0	0.039	12	60.0	0.338	13	65.0	0.705	15	75.0	0.098
Total, H	193	88	45.6		87	45.1		106	54.9		86	46.5	
Total, L	39	26	66.7	0.017	24	61.5	0.068	21	53.8	0.624	24	63.2	0.348
Completer analysis, N = *196*													
Males, H	35	20	57.1		12	34.3		14	40.0		21	61.8	
Males, L	17	10	58.8	0.866	10	58.8	0.537	7	41.2	0.778	7	46.7	0.537
Females, H	130	66	50.8		71	54.6		78	59.5		63	51.2	
Females, L	14	12	85.7	0.025	11	78.6	0.579	9	64.3	0.850	13	92.9	0.026
Total, H	165	86	52.1		83	50.3		92	55.4		84	53.5	
Total, L	31	22	71.0	0.048	21	67.7	0.874	16	51.6	0.487	20	69.0	0.235

Abbreviations: CGI, Clinical Global Impression; HAMA, Hamilton Anxiety Scale; LOCF, last observation carried forward; MI, Mobility Inventory; *MAOA*, *monoamine oxidase A*.

behavioral avoidance test



Personalized Psychiatry & Panic Disorder:

Neuroimaging

Neural Substrates of Treatment Response to Cognitive-Behavioral Therapy in Panic Disorder With Agoraphobia

Ulrike Lueken, Ph.D.

Benjamin Straube, Ph.D.

Carsten Konrad, M.D.

Hans-Ulrich Wittchen, Ph.D.

Andreas Ströhle, M.D.

André Wittmann, Dipl.-Psych.

Bettina Pfleiderer, M.D., Ph.D.

Christina Uhlmann, Ph.D.

Volker Arolt, M.D.

Andreas Jansen, M.D.

Tilo Kircher, M.D.

Objective: Although exposure-based cognitive-behavioral therapy (CBT) is an effective treatment option for panic disorder with agoraphobia, the neural substrates of treatment response remain unknown. Evidence suggests that panic disorder with agoraphobia is characterized by dysfunctional safety signal processing. Using fear conditioning as a neurofunctional probe, the authors investigated neural baseline characteristics and neuroplastic changes after CBT that were associated with treatment outcome in patients with panic disorder with agoraphobia.

Method: Neural correlates of fear conditioning and extinction were measured using functional MRI before and after a manualized CBT program focusing on behavioral exposure in 49 medication-free patients with a primary diagnosis of panic disorder with agoraphobia. Treatment response was defined as a reduction exceeding 50% in Hamilton Anxiety Rating Scale scores.

Results: At baseline, nonresponders exhibited enhanced activation in the right pregenual anterior cingulate cortex, the hippocampus, and the amygdala in response to a safety signal. While this activation pattern partly resolved in nonresponders after CBT, successful treatment was characterized by increased right hippocampal activation when processing stimulus contingencies. Treatment response was associated with an inhibitory functional coupling between the anterior cingulate cortex and the amygdala that did not change over time.

Conclusions: This study identified brain activation patterns associated with treatment response in patients with panic disorder with agoraphobia. Altered safety signal processing and anterior cingulate cortex-amygdala coupling may indicate individual differences among these patients that determine the effectiveness of exposure-based CBT and associated neuroplastic changes. Findings point to brain networks by which successful CBT in this patient population is mediated.

(Am J Psychiatry 2013; 170:1345–1355)

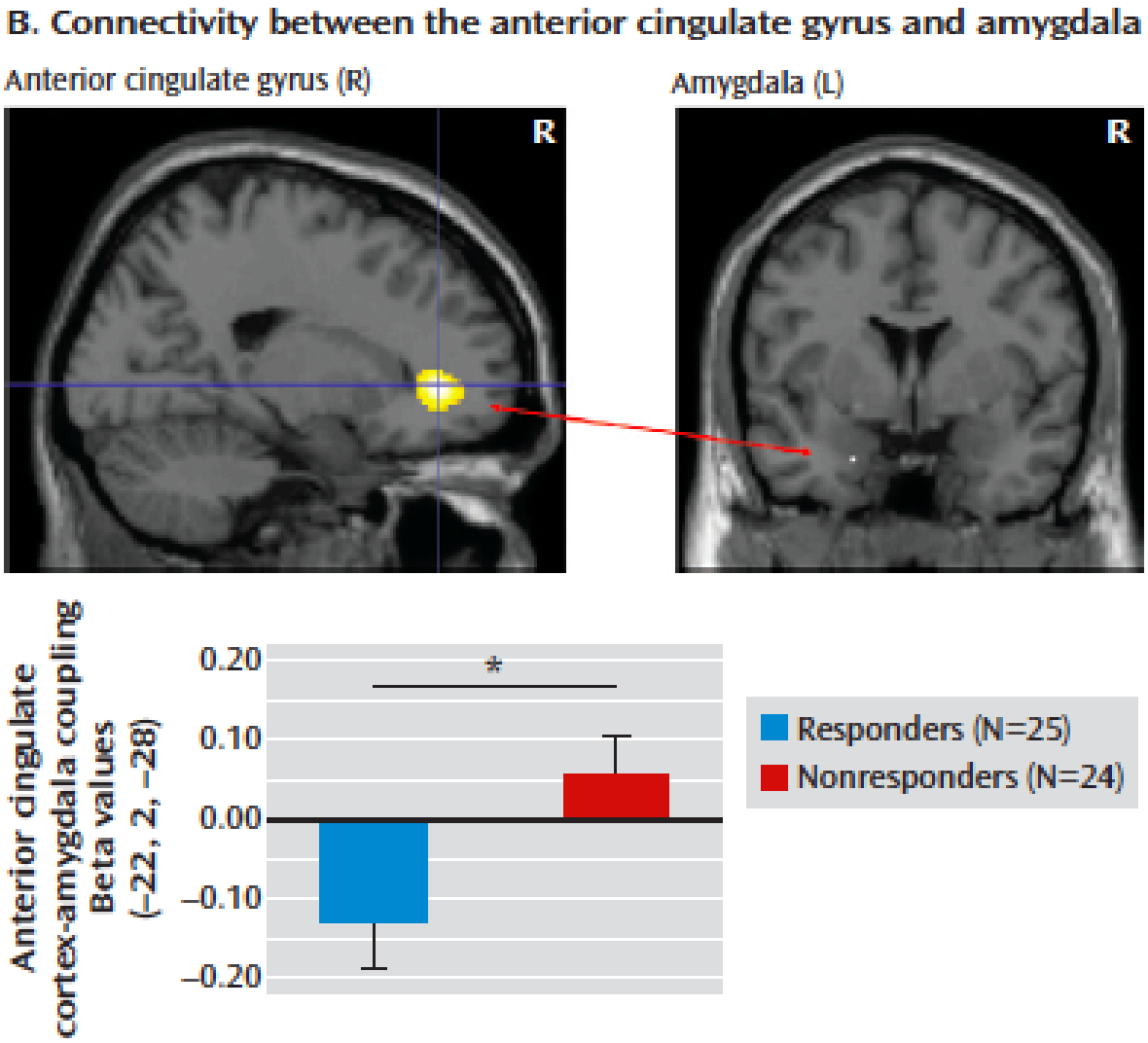


FIGURE 1. Differences in Functional Brain Activation During the Fear-Conditioning Task in Responders (N=25) and Nonresponders (N=24) Before Cognitive-Behavioral Therapy[a]

Neuropsychopharmacology (2014) 39, 1254–1261

www.neuropsychopharmacology.org

Single-Subject Anxiety Treatment Outcome Prediction using Functional Neuroimaging

Tali M Ball*[,1,2], Murray B Stein[1,3,4], Holly J Ramsawh[5], Laura Campbell-Sills[1] and Martin P Paulus[1,3]

[1]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA; [2]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA; [3]Psychiatry Service, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA; [4]Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA, USA; [5]Department of Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Random forest model

Greater activation in cortico-limbic circuitry predicts better CBT response

Personalized Psychiatry & Panic Disorder:

Respiration

Panic Disorder Respiratory Subtype: Psychopathology, Laboratory Challenge Tests, and Response to Treatment

Rafael C. Freire, MD, MSc, Giampaolo Perna, MD, PhD, and Antonio E. Nardi, MD, PhD

Table 2. Differences Between the Respiratory and Nonrespiratory

Evidence type	Respiratory subtype	Nonrespiratory subtype
Familial history of PD	+	−
Comorbidity with depression	−	+
Duration of illness	+	−
Scores in panic disorder severity scales	+	−
Sensitivity to CO_2 challenge tests	+	−
Sensitivity to breath-holding challenge tests	+	−
Sensitivity to hyperventilation challenge tests	+	−
Sensitivity to caffeine challenge tests	+	−

Psychological Medicine (2012), **42**, 461–474. © Cambridge University Press 2011
doi:10.1017/S0033291711001425

ORIGINAL ARTICLE

A latent class approach to the external validation of respiratory and non-respiratory panic subtypes

R. Roberson-Nay*, S. J. Latendresse and K. S. Kendler

Virginia Commonwealth University, Virginia Institute for Psychiatric and Behavioral Genetics, P.O. Box 980489, Richmond, VA 23298, USA

Conclusions. These data suggest that respiratory and non-respiratory panic represent valid subtypes along the PD continuum, with the respiratory variant representing a more severe form of the disorder.

British Journal of Psychiatry (1993), **163**, 201–209

Subtyping of Panic Disorder by Symptom Profile

ANDREW C. BRIGGS, DAVID D. STRETCH and SYDNEY BRANDON

During Phase II of the Cross-National Panic Study, descriptions of the patient's last severe panic attack were collected for 1168 patients. Statistical analysis indicated that patients could be divided into two groups, characterised by the presence or absence of prominent respiratory symptoms. The two groups did not differ on demographic variables or coexisting diagnoses, but they did differ on psychopathology on entry to the study and treatment outcome. The group with prominent respiratory symptoms suffered more spontaneous panic attacks and responded to imipramine, whereas the group without prominent respiratory symptoms suffered more situational panic attacks and responded more to alprazolam. It is important to distinguish spontaneous and situational panic attacks, to aid choice of treatment.

0271-0749/02/2203-0300/0
Journal of Clinical Psychopharmacology

Vol. 22, No. 3
Printed in U.S.A.

Antipanic Drug Modulation Of 35% CO_2 Hyperreactivity and Short-Term Treatment Outcome

GIAMPAOLO PERNA, MD, PHD, ANGELO BERTANI, MD, DANIELA CALDIROLA, MD, ANGELA GABRIELE, MD, SILVIA COCCHI, MD, AND LAURA BELLODI, MD

The Anxiety Disorder Clinical and Research Unit, Department of Neuropsychiatric Sciences, University of Milan, Istituto Scientifico Ospedale San Raffaele, Milan, Italy

Decreased CO_2 hyperreactivity after one week (Δ 7 POST-VAS) was the only significant predictor for the clinical outcome after one month for all measures considered (Δ% PASS: β: .40 ± .12, $p < .001$; Δ% FQ: β: .31 ± .12, $p < .02$ and Δ% SDS: β: .26 ± .12, $p < .05$),

Clinical outcome after 1 month of treatment

Paroxetine
Sertraline
> Fluvoxamine

Psychiatry Research 219 (2014) 311–315

Contents lists available at ScienceDirect

Psychiatry Research

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

Low baseline pCO_2 predicts poorer outcome from behavioral treatment: Evidence from a mixed anxiety disorders sample

Carolyn D. Davies*, Michelle G. Craske

Department of Psychology, University of California, Los Angeles (UCLA), 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, USA

Journal of Psychiatric Research 47 (2013) 1357–1362

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

Phosphate levels as a possible state marker in panic disorder: preliminary study of a feasible laboratory measure for routine clinical practice

Lucía Pérez-Costillas [a,1], M. Rosa Montes [b], José M. Martínez-Ortega [c,d], María Dolores Carretero [c], Luis Gutiérrez-Rojas [a,d], Manuel Gurpegui [c,d,*]

[a] Psychiatry Service, San Cecilio University Hospital, Granada, Spain
[b] Department of Physiology, Institute of Neurosciences, University of Granada, Granada, Spain
[c] Department of Psychiatry, University of Granada, Granada, Spain
[d] CTS-549 Research Group, Institute of Neurosciences, Center for Biomedical Research (CIBM), University of Granada, Granada, Spain

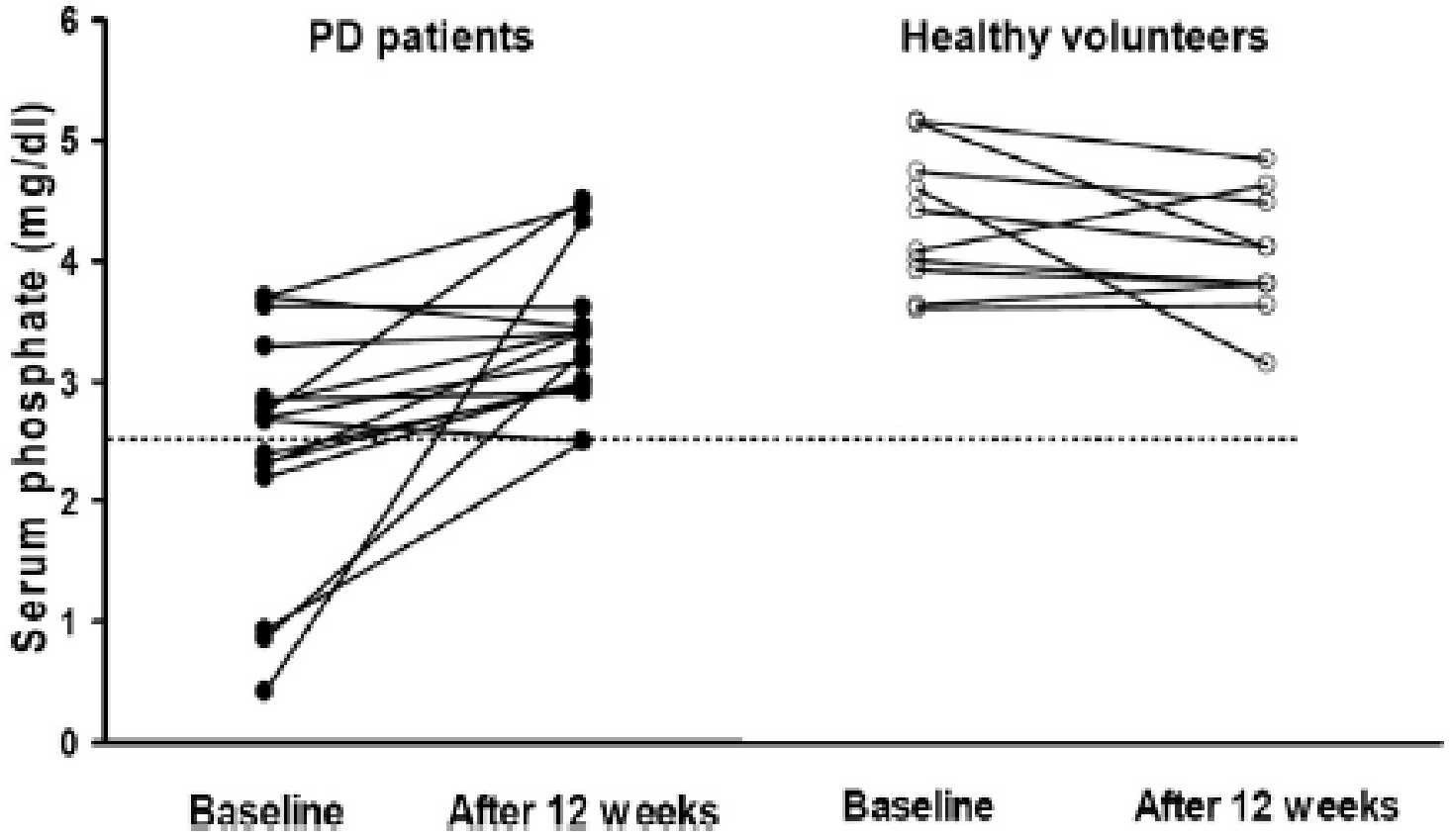
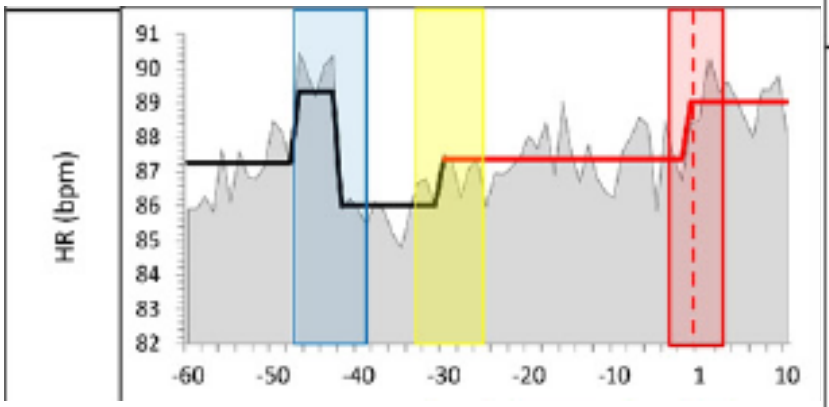


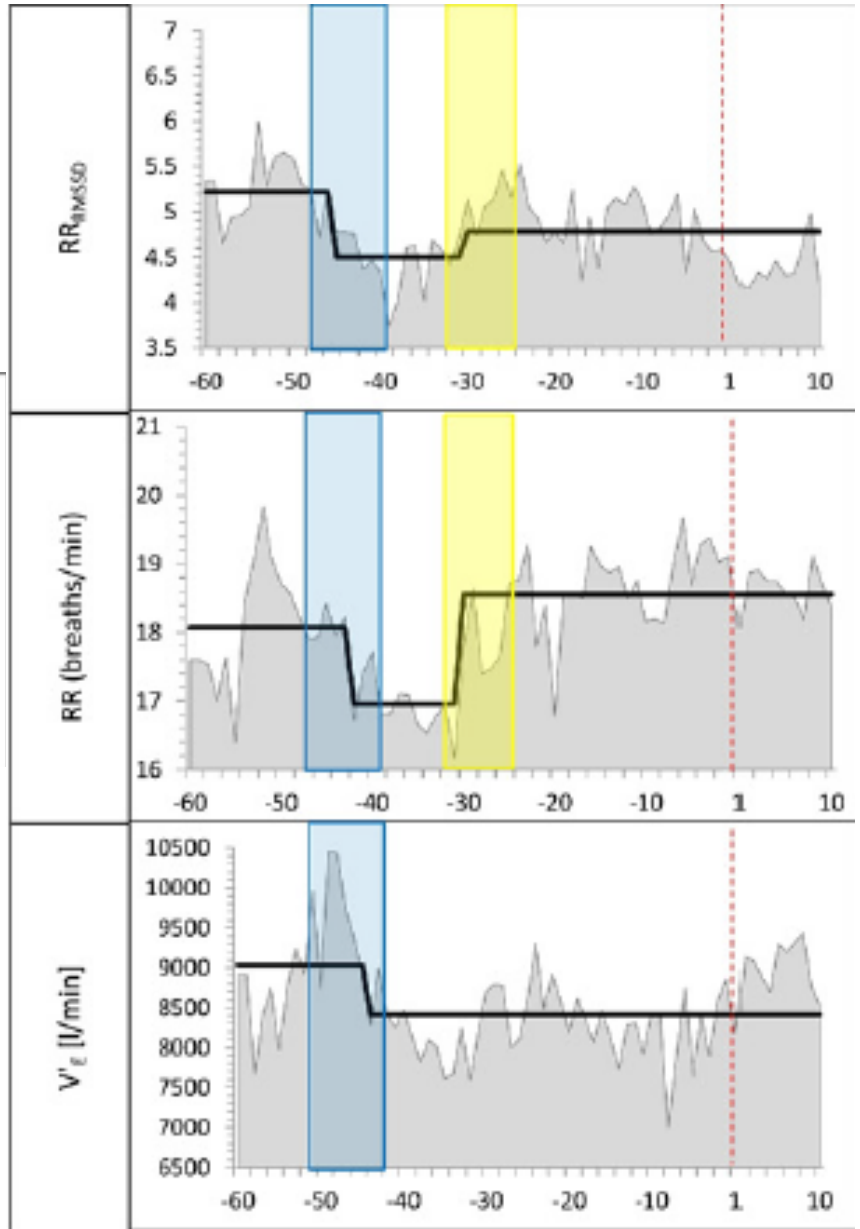
Fig. 1. Serum phosphate levels in 16 panic disorder (PD) patients and 10 healthy volunteers at baseline and after 12 weeks of successful treatment (in patients) or a similar period in the control group.

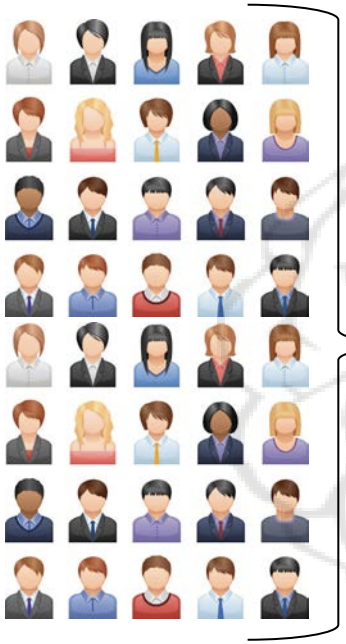
Do Unexpected Panic Attacks Occur Spontaneously?

Alicia E. Meuret, David Rosenfield, Frank H. Wilhelm, Enlu Zhou, Ansgar Conrad, Thomas Ritz, and Walton T. Roth

BIOL PSYCHIATRY 2011;70:985–991







Ideas for new predictors

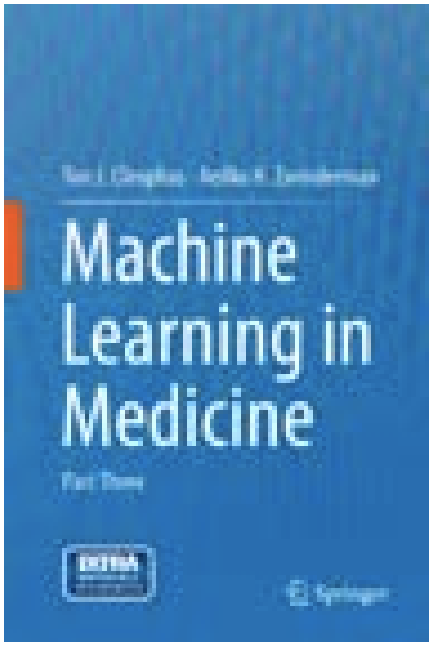
Challeging personal models

Personalized Psychiatry Studies

Better Personalized Psychiatrist !

The future…..?

Machine Learning for Personalized Medicine



Machine Learning: Supervised Artificial Neural Networks

These are AI systems doesn't work according to predetermined general decision algorithms and rules (as guidelines do for the "average" patients). Instead they can provide personalized predictions and suggest clinical decisions tailored on the individual characteristics of each individual, joining the ability to handle the complexity of real clinical cases and the rigor of algorithms.

The techniques are able to learn and modellize them starting from a certain amount of so-called training cases.