ECNP neuroscience applied

ECNP SEMINAR

IN NEUROPSYCHOPHARMACOLOGY

30 October – 1 November 2015

Esposende, Portugal

INTRODUCTION

The European College of Neuropsychopharmacology (ECNP) was established in 1987 on the initiative of scientists and clinicians working in Europe in the convergent disciplines in neuropsychopharmacology and related neurosciences.

ECNP is an independent, non-governmental, scientific association dedicated to the science and treatment of disorders of the brain. Founded in 1987, its goal is to bring together scientists and clinicians to facilitate information-sharing and spur new discoveries.

The objective of ECNP is to serve the public good by stimulating high-quality experimental and clinical research and education in applied and translational neuroscience. It seeks to do this by:

•Co-ordinating and promoting scientific activities and consistently high-quality standards between countries in Europe.

•Bringing together all those involved in or interested in the scientific study of applied and translational neuroscience by arranging scientific meetings, seminars, and study groups.

•Providing guidance and information to the public on matters relevant to the field.

•Providing a format for the co-ordination and for development of common standards in Europe.

To fulfill this aim ECNP organizes, amongst others, yearly the ECNP Congress that comprises of 6 plenary lectures, 28 symposia and 7 educational update sessions. The annual meeting attracts more than 6,000 participants and is considered to be the largest event in neuropsychopharmacology in Europe.

ECNP organizes seminars, as the one you have been invited to participate, in areas of Europe where there are less opportunities for psychiatrists to participate in international meetings. Interaction is the keyword at these meetings and they have proved very successful both for the participants and for the experts. During the seminar we discuss clinical and research issues that the local organizers feel that are needed to be covered and using these

topics as a model for teaching how to ask a research question and how to plan an effective study. Leading ECNP experts that are also talented speakers will facilitate mutual discussion in small groups allowing you to present your abstract and get feedback from your colleagues and local mentors.

So far, ECNP has organized this meeting in Poland, Estonia, Turkey, Bulgaria, Slovak Republic, Hungary, Czech Republic, Moldova, Romania, Greece, Russia, Latvia and recently in Macedonia, Armenia, Georgia and Serbia. In some countries we have organized it more than once.

ECNP also supports on an annual basis participation of 100 junior scientists and researchers in an intensive three-day Workshop in Nice. Other educational activities of ECNP include the journal European Neuropsychopharmacology that promotes scientific knowledge along with publishing consensus statements. . In addition, since 2009 ECNP organizes a summer school of neuropsychopharmacology in Oxford, since 2012 a school of child and adolescent neuropsychopharmacology in Venice and since 2013 a school of old age neuropsychopharmacology in Venice.

Last year we started with a pilot of a new initiative, The ECNP Research Internship. This is a new collaborative initiative of ECNP and the ECNP Junior Member Advisory Panel (JMAP) that aims to provide short-term research internship opportunities for junior researchers. Senior researchers from the list of ECNP Fellow members offer unpaid 2 week exploring research internship in their institutions.

Please see the ECNP website (www.ecnp.eu) where you can find information about all the above initiatives and additional information and look for the activity that fits you.

I look forward to a fruitful and inspiring meeting in Portugal!

Gil Zalsman

Chair ECNP Educational Committee

PROGRAMME

FRIDAY 30 OCTOBER 2015

Arrival of participants and experts

19.00 Welcome and dinner

SATURDAY 31 OCTOBER 2015

09:00 – 09:15 What is ECNP?
Introductions to the programme
Carmen Moreno, Seminar leader, Spain

09:15 – 10:00 A new approach to treatment of psychosis and clinical pharmacology of antipsychotics
Carmen Moreno, Spain

10:00 – 10:45 OCD treatment as a model for neuropsychopharmacology research
Koen Schruers, The Netherlands

10:45 – 11:30 Cofee break

11:30 – 12:15 Maintenance treatment of bipolar disorder- focus on the polarity index
Dina Popovic, Spain

12:15 – 12:30 How to prepare a scientific presentation?
Carmen Moreno, Spain

12:30 – 13:30 Lunch

Presentations participants in 3 groups in 3 parallel workshops			
Round 1 13.30 – 15.00	Carmen Moreno and Joao Bessa Group 1	Koen Schruers and Albino Oliveira- Maia Group 2	Dina Popovic and Frede rico Simões Couto Group 3

15:00 – 15:15 Break

12:30 – 13:30 How to prepare a manuscript?

Carmen Moreno, Spain

16:00 – 16:30 Panel discussion:

How to prepare a clinical research project?

Chair: Carmen Moreno

Panel members: Koen Schruers and Dina Popovic

17:00 – 21:00 Social activity, group photo and dinner

SUNDAY 1 NOVEMBER 2015

Presentations participants in 3 groups in 3 parallel workshops			
Round 2 08.30 – 10.00	Carmen Moreno and Joao Bessa Group 2	Koen Schruers and Albino Oliveira- Maia Group 3	Dina Popovic and Frederico Simões Couto Group 1
10.00 – 10.30 Coffee break			
Round 3 10.30 – 12.00	Carmen Moreno and Joao Bessa Group 3	Koen Schruers and Albino Oliveira- Maia Group 1	Dina Popovic and Frederico Simões Couto Group 2
12.00 – 14.00 Lunch and preparation for plenary session			
Plenary 14.00 – 15.00	14.00 – 14.20	Group 1 Presentation and discussion	
	14.20 – 14.40	Group 2 Presentation and discussion	
	14.40 – 15.00	Group 3 Presentation and discussion	

15:00 – 15:15 Short Break

Preparation of the awards ceremony

15:15 – 15:30 Awards ceremony

15:30 – 15:45 Concluding remarks and thanks

Carmen Moreno and João Bessa

FACULTY

CARMEN MORENO

Dr. Carmen Moreno (MD, PhD) is a Child Psychiatrist and Associate Professor of the Gregorio Marañón Psychiatry Department and Complutense University School of Medicine, Madrid, Spain. Dr. Moreno completed her MD and PhD degrees at Autónoma University and Complutense University in Madrid, followed by a Research Fellowship in Child and Adolescent Psychiatry at Columbia University, New York, USA. Dr. Moreno has been focusing her career on early-onset psychiatric disorders, mainly psychotic and affective disorders, and recently also other neurodevelopmental disorders. She is recognized by her studies in raising awareness of misdiagnosis of bipolar disorder in children and adolescents. Dr. Moreno is actively involved on research projects exploring key biological aspects of early-onset psychiatric disorders, including multimodal neuroimaging, intermediate mechanisms such as inflammation and oxidative stress, and metabolomics. Her efforts are also focused on exploring secondary effects of psychopharmacological interventions towards development of new treatment interventions in young patients, being currently involved on independent clinical studies with PUFAS omega-3 and N-acetilcysteine. Dr. Moreno has authored more than 30 peer-reviewed publications. She was awarded the ECNP Research Felllowship Award, and the Awards for Young Scientists and Senior Scientists of the Spanish Association of Biological Psychiatry. She is member of the ECNP, where she serves in the Membership Committee, and is Co-chair of the ECNP Adolescent Child and Adolescent Neuropsychopharmacology Network.

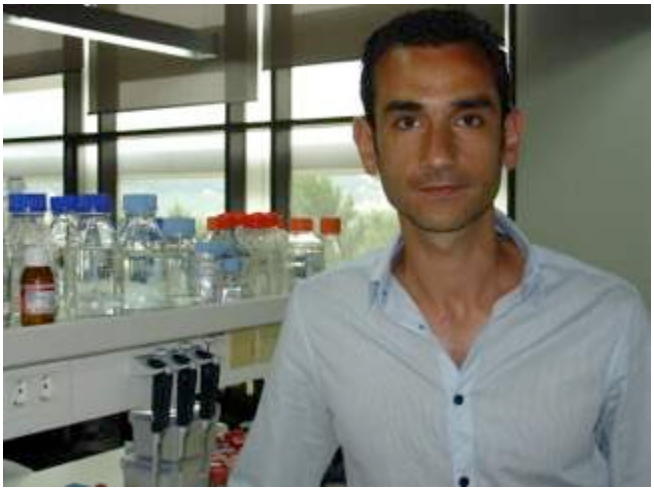
KOEN SCHRUERS

Koen R.J. Schruers, MD PhD, is a psychiatrist and associate professor at Maastricht University, The Netherlands were he heads the research group on affective neuroscience at the Research Institute of Mental Health and Neuroscience. He combines clinical and neurobiological expertise in the study of human and animal models of fear and panic. He teaches in the PhD training program and at the master programs of medicine, neuroscience and psychology. He is also executive director of the International Postgraduate Master Program in Affective Neuroscience (www.affect-neuroscience.org)
Clinically, he heads the treatment program for anxiety, OCD and PTSD of Mondriaan Mental Health Center/Maastricht University.

DINA POPOVIC

Dr. Dina Popovic has received her degree in Medicine, *cum laude*, from the University of Bologna (Italy), has specialized in Psychiatry and was awarded a PhD with European label at the University of Pisa. Alongside with active clinical practice Dr. Dina Popovic performs clinical research at Bipolar Disorders Program of Hospital Clinic, University of Barcelona, Spain, headed by Prof. Eduard Vieta. Her scientific interests and publications primarily include Mood Disorders, Psychotic Disorders and Dual Pathology, with a special focus on clinical, pharmacological, genetic and neurophysiological aspects.

JOÃO BESSA



João Bessa has a Medical Degree (MD) by the Oporto Medical School (FMUP – Faculdade de Medicina da Universidade do Porto), and a clinical speciality in Psychiatry (Hospital de Braga, 2009). He received his PhD in Neurosciences at the Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho in 2008.

He works as a researcher in the Neuroscience Domain of the Life and Health Sciences Research Institute (ICVS) since 2005, where he currently works as a Research Project Coordinator. His main research interests include the neurobiological mechanisms involved in the pathophysiology of psychiatric disorders, in particular of depression. He has been focused in the role of neuroplastic phenomena in the genesis and recovery from depression, using animal models of chronic stress and the administration of antidepressive drugs.

He is author or co-author of several publications in international journals, book chapters and has participated in numerous international meetings and symposia in the fields of Neurosciences and Psychiatry with oral and poster presentations. He has received 6 awards for his scientific work. In addition he collaborates as referee for several publications in the field of Biological Psychiatry.

He has been involved in educational activities in the School of Health Sciences since 2003. He currently works as Assistant Professor in the basic fields of Anatomy in the Organic and Functional Systems curricular area and as Coordinator in the clinical field of Psychiatry in the Clinical Neurosciences curricular area. In addition he has participated as oral presenter in several post-graduation courses in the field of Neurosciences at the ICVS and as poster presenter in international meetings of Medical Education.

ALBINO OLIVEIRA MAIA

Albino Oliveira Maia completed his medical degree at the Porto University School of Medicine in July 2002, where he later defended a doctorate in neuroscience. His doctoral thesis was developed from 2005 to 2008 in Duke University, under the supervision of Prof. Miguel Nicolelis. He stayed at Duke as a postdoctoral fellow, and returned to Portugal in 2010 to start a residency training programme at the Department of Psychiatry and Mental Health of Centro Hospitalar de Lisboa Ocidental.
Currently, he also coordinates the Neuropsychiatry Unit at the Champalimaud Clinical Centre and Neuroscience Programme, and is Invited Professor at the NOVA School of Medicine. Albino's research has been devoted to understanding how food activates brain reward circuits and, more recently, how these mechanisms could be relevant for compulsive behaviors.
His work has been published in journals such as *Neuron* and *Proceedings of the National Academy of Sciences of the USA* and he has received prizes and scholarships from several national and international institutions, such as Fundação para a Ciência e Tecnologia, AXA Fund, Fundação Calouste Gulbenkian, Sociedade Portuguesa de Neurociência, Sociedade Portuguesa de Psiquiatria e Saúde Mental, International and European Associations for the Study of Obesity and the Harvard Medical School – Portugal Programme.

FREDERICO SIMÕES COUTO

1. Education

1991-1997 MD, Lisbon Faculty of Medicine, Lisbon, Portugal
2010- PhD student, Faculty of Medicine, Lisbon, Portugal

2. Hospital Activity

1998-1999 Rotating Internship, Santo António dos Capuchos Hospital, Lisbon.
2000-2005 Psiquiatry Residency, Santa Maria Hospital.
2005 Honorary Senior House Officer on Psychiatry at the Maudsley Hospital, London (3 months)
2005- Psychiatrist, Hospital de Santa Maria, Lisbon. Inpatient and outpatient clinics, day hospital, emergency service, electroconvulsive therapy, and training of interns. Responsible for the implementation of the Deep Brain Stimulation treatment (psychiatry) for psychiatric disorders.
Main areas of interest: general psychiatry and dementia.

3. Teaching Activity

1997-99 Pharmacology Monitor of Lisbon Faculty of Medicine
1999- Pharmacology Assistant of Lisbon Faculty of Medicine
2004- Psychiatry Assistant of Lisbon Faculty of Medicine

4. Research Activity

a) Preclinical

1995-2003 Center of Experimental and Clinical Pharmacology of University of Lisbon.
2003- Institute of Pharmacology and Neurosciences of Institute of Molecular Medicine, Lisbon. Specially animal behavioral studies on depression.

b) Clinical

1995- Dementia Study Group of Institute of Molecular Medicine, Lisbon. Includes several projects on Alzheimer's disease, mild cognitive impairment and on the relation between depression and dementia.

5. Other activities

2012- Psychiatry consultant for Caixa Geral de Aposentações (retirement national agency for civil servants) and for Social Security

LECTURES

CARMEN MORENO

A NEW APPROACH TO TREATMENT OF PSYCHOSIS AND CLINICAL PHARMACOLOGY OF ANTIPSYCHOTICS

Development of antipsychotic treatments has been focusing until recently on dopamine pathways known to be altered in psychosis. In fact, following initial serendipity clinical observation, most antipsychotic drugs have been developed targeting D2 dopamine receptors. D2 blockade is related to clinical efficacy measured as improvement in positive psychotic symptoms, but is also related to adverse events such as extrapyramidal symptoms, impairment of negative symptoms, and worsening on cognition. Positive symptoms are most easily recognized in the acute setting, but negative and cognitive symptoms are pervasive on most psychotic disorders, have great impact on long-term functioning and increase the complexity of treatment. Biological and psychological factors, including medical and psychiatric comorbidities, have also great impact on functionality, and adverse events such as weight gain and sedation may worsen them. New insights suggest that treatment approaches to psychosis need to move from the single-disease paradigm and the search of new medications based on the mechanism of action of the old ones, towards treatment development using experimental medicine methods based on new target identification, and aiming at domains of brain function relevant to psychopathology across different units of analysis (such as genes, circuits or behaviors). Preventive strategies such as primary prevention of vulnerability or treatment at vulnerability stages previous to psychosis onset are currently being studied with promising initial results.

ECNP

A new approaches to treatment of psychosis and clinical pharmacology of antipsychotics

Carmen Moreno MD, PhD
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Disclosure:
Carmen Moreno M.D., Ph.D.

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Instituto de Salud Carlos III, Spanish Spanish Ministry of Economy and Competitiviness	X	X
CIBERSAM		x
Janssen-Cilag	X	
Otsuka	X	
AstraZeneca	X	
Bristol-Myers Squibb	X	

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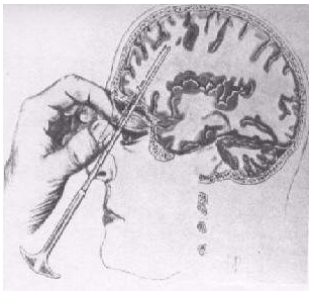
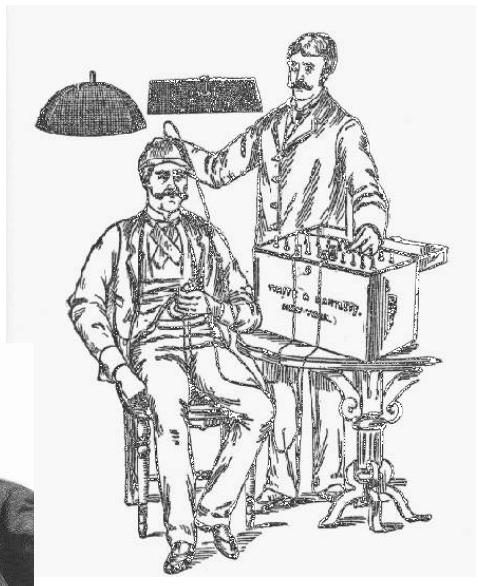
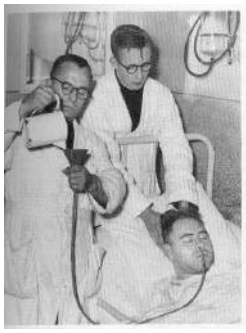
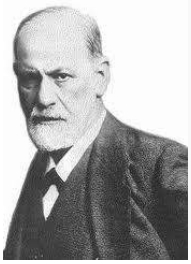
- Barriers for drug discovery
- New paradigms

19th and 20th Centuries:
New approaches to treatment of schizophrenia







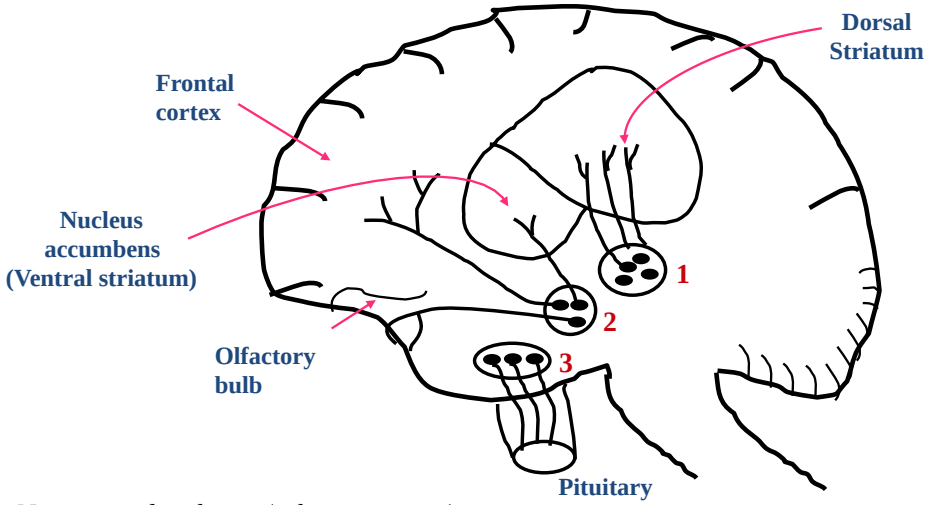


- 19th century: the discovery of phenothiazines has its origin in the development of German dye industry

- Up to 1940 they were employed as antiseptics, antihelminthics and antimalarials

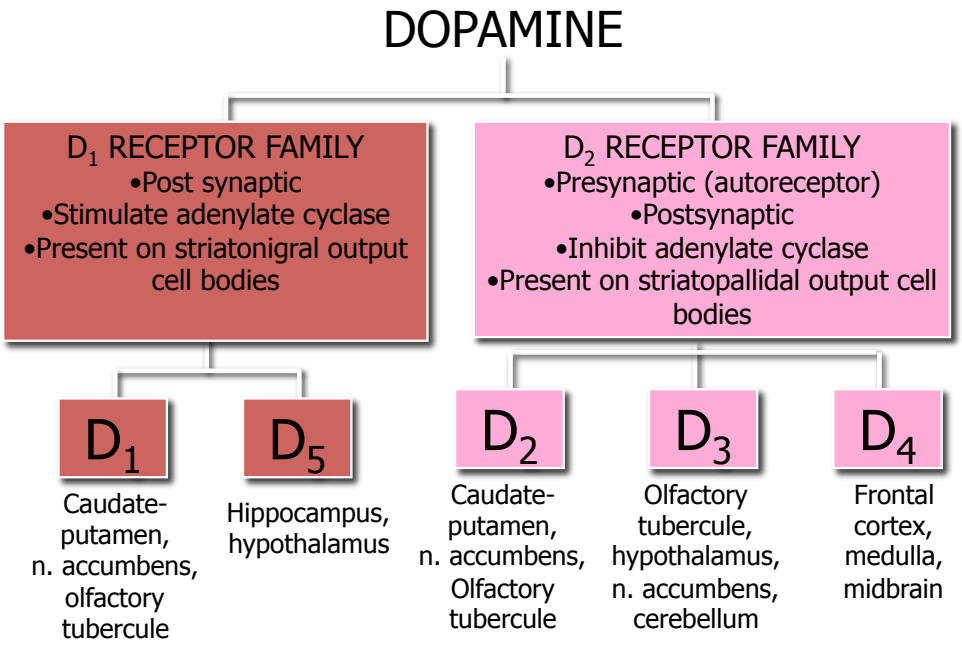
- Finally, in the context of research on antihistaminic substances in France after World War II chlorpromazine was used in anaesthesiology

Dopamine pathways



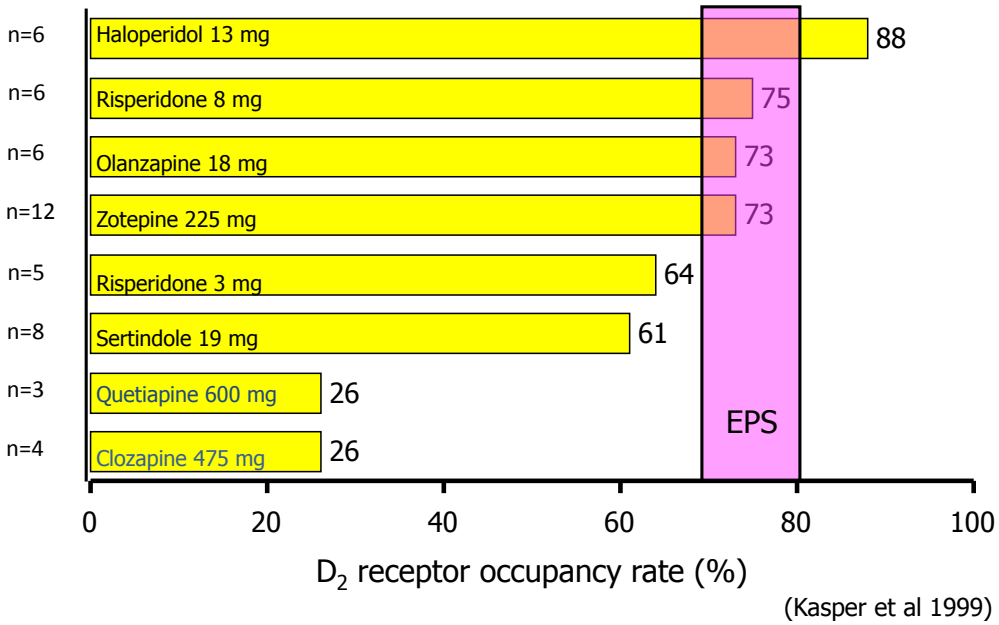
1. Nigrostriatal pathway (substantia nigra)
   Parkinson's disease, initiation of motor plans
2. Mesocortical and mesolimbic pathways (Ventral tegmental area: VTA)
   Psychosis, reward and motivation
3. Tuberoinfundibular pathway (Median eminence)
   Prolactin release

Classification of Dopamine Receptors

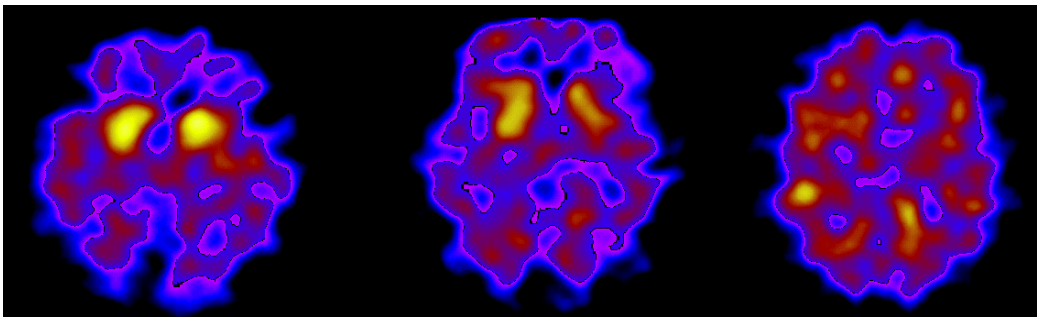


Conventional & New Antipsychotics

Striatal D_2 receptor occupancy rates



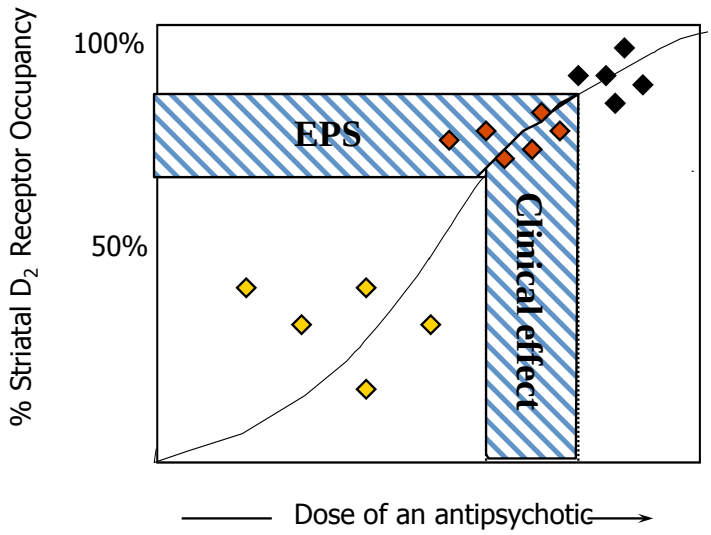
(Kasper et al 1999)



Healthy Volunteer | Clozapine treated Schizophrenia patient | Typical antipsychotic treated schizophrenia patient

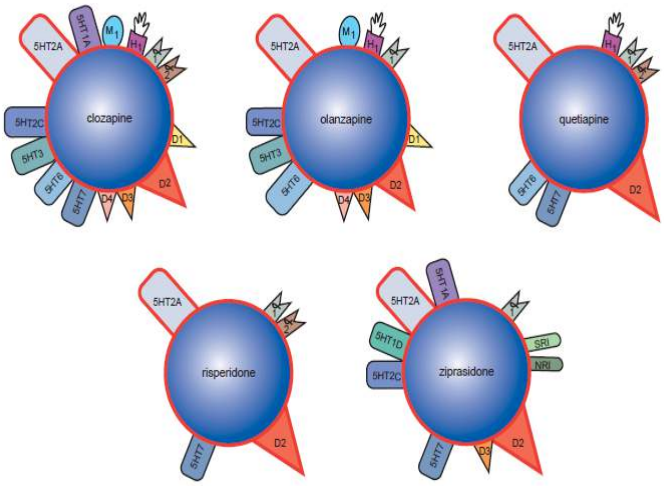
^{123}I-IBZM SPET scans of striatal D_2 receptor occupancy
(Pilowsky et al 1992)

Relationship between D_2 receptor occupancy, EPS and response



(after, Farde et al, 1992, Nyberg et al 1996, Pickar et al 1996 & Kapur et al 2000)

New antipsychotics: Pharmacokinetic heterogeneity



Stahl, J Clin Psychiatry 2003

PSYCHOSIS AND FEVER

There are other things besides positive symptoms!!

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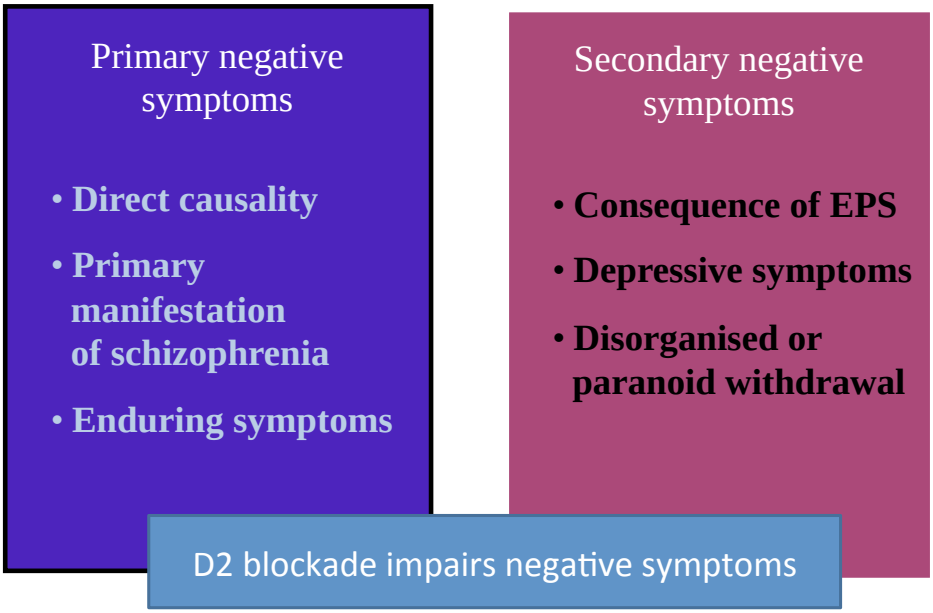
- **Barriers for drug discovery**
- New paradigms

Barriers to Drug Discovery:
Reasons for Minimal Progress since 1952

Adherence to single disease paradigm where psychosis represents the latent disease structure.

Discovery platforms produce dopamine antagonists.

Negative symptoms of schizophrenia



Arango et al 2004, Artaloyta et al 2008

Antipsychotics and negative symptoms

- SGA do not seem to improve primary enduring negative symptoms (Arango et al 2004)

- Patients with negative symptoms are at higher risk to develop Metabolic Syndrome (Arango et al 2008)

D2 Blockade: negative symptoms in healthy controls

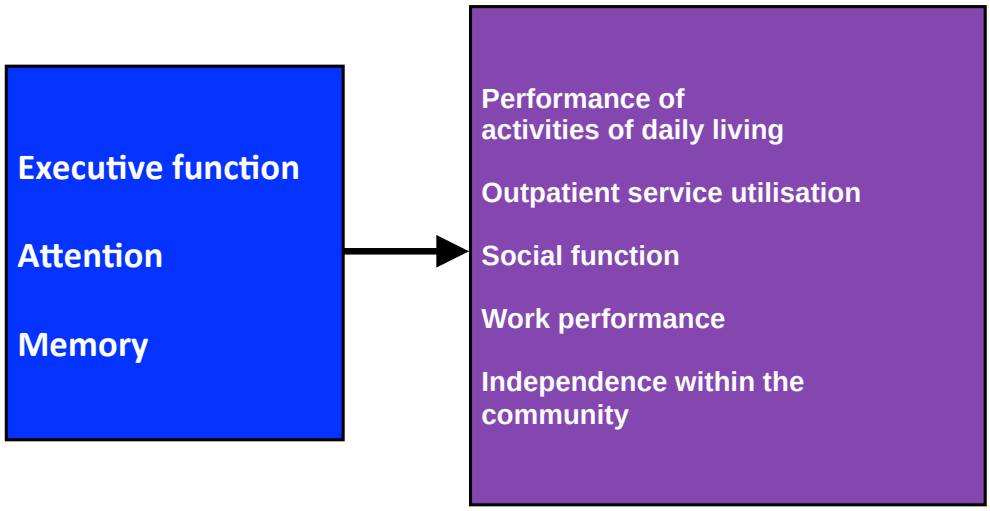
TABLE 2. Differences Between Treatments in Motor Signs and Negative Symptoms of 32 Healthy Subjects Given Placebo, Haloperidol, and Risperidone Individually[a]

		Haloperidol Versus Placebo			Risperidone Versus Placebo			Risperidone Versus Haloperidol		
Variable	ANOVA (p)	Difference in Score	96% CI	p	Difference in Score	96% CI	p	Difference in Score	96% CI	p
Simpson-Angus Rating Scale		0.07	−0.40 to 0.54	0.77	−0.07	−0.45 to 0.31	0.72	−0.13	−0.51 to 0.24	0.48
Handwriting area	0.29	2.50	−2.83 to 7.82	1.00	4.80	−1.24 to 10.80	0.36	2.30	−4.55 to 9.14	1.00
No control for drowsiness										
Brief Psychiatric Rating Scale (BPRS)	<0.001	1.13	−0.05 to 2.31	0.06	2.20	1.02 to 3.38	<0.001	1.07	−0.11 to 2.25	0.09
Scale for the Assessment of Negative Symptoms (SANS)		0.63	0.01 to 1.25	0.04	1.10	0.48 to 1.72	<0.001	0.47	−0.15 to 1.08	0.21
Subjective Deficit Syndrome Scale	<0.001	8.13	3.47 to 12.80	<0.001	9.70	5.04 to 14.40	<0.001	1.57	−3.10 to 6.23	1.00
Analog scale	<0.001	23.86	6.54 to 41.20	0.004	46.21	28.90 to 63.50	<0.001	22.35	5.03 to 39.70	0.007
Drowsiness	<0.001	5.01	1.74 to 8.28	0.001	9.04	5.76 to 12.30	<0.001	4.03	0.75 to 7.30	0.01
Control for drowsiness										
BPRS	<0.03	0.94	−0.38 to 2.27	0.25	1.86	0.25 to 3.46	0.02	0.91	−0.36 to 2.19	0.25
SANS		0.58	−0.12 to 1.29	0.13	1.01	0.17 to 1.86	0.01	0.43	−0.25 to 1.10	0.37
Subjective Deficit Syndrome Scale	0.06	4.42	−0.08 to 8.93	0.06	3.01	−2.43 to 8.44	0.53	−1.42	−5.75 to 2.92	1.00
Analog scale	0.22	4.62	−8.85 to 18.10	1.00	11.50	−4.76 to 27.80	0.26	6.89	−6.10 to 19.90	0.59

[a] ANOVA was not applied to the Simpson-Angus Rating Scale or the SANS. No analysis was performed for the Barnes Ratings Scale for Drug-Induced Akathisia because only three patients rated a 1 on this scale (two subjects taking haloperidol and one taking risperidone).

Artaloytia et al 2006

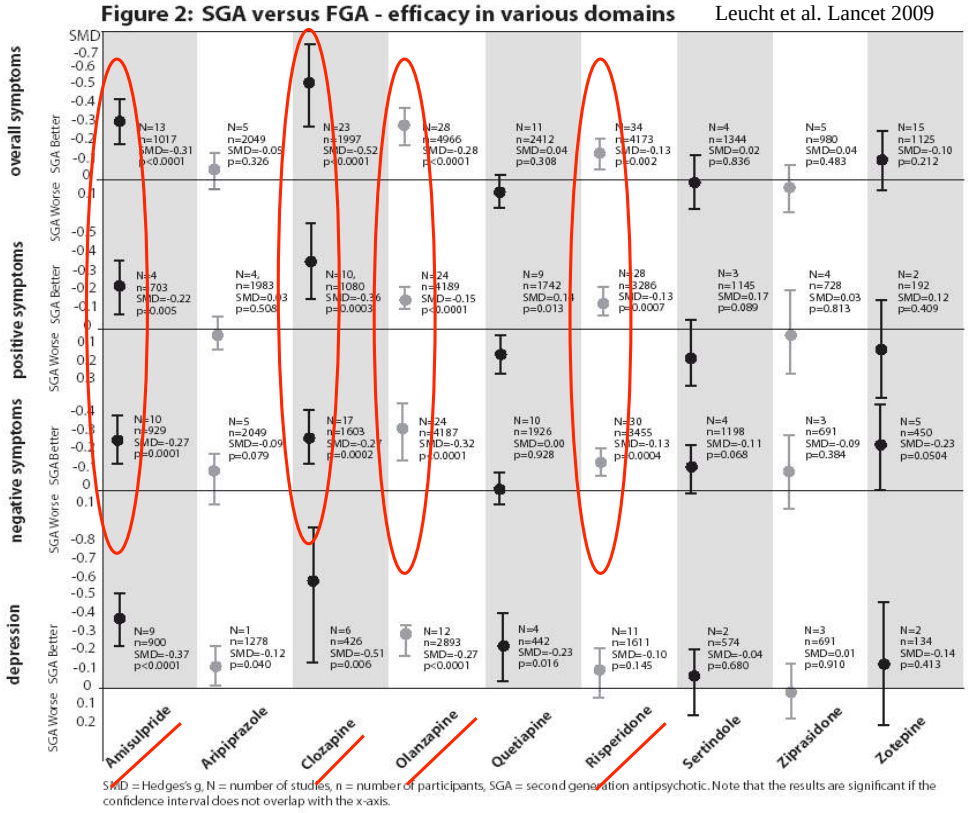
Cognitive deficits predict functional outcomes



D2 blockade impairs cognition

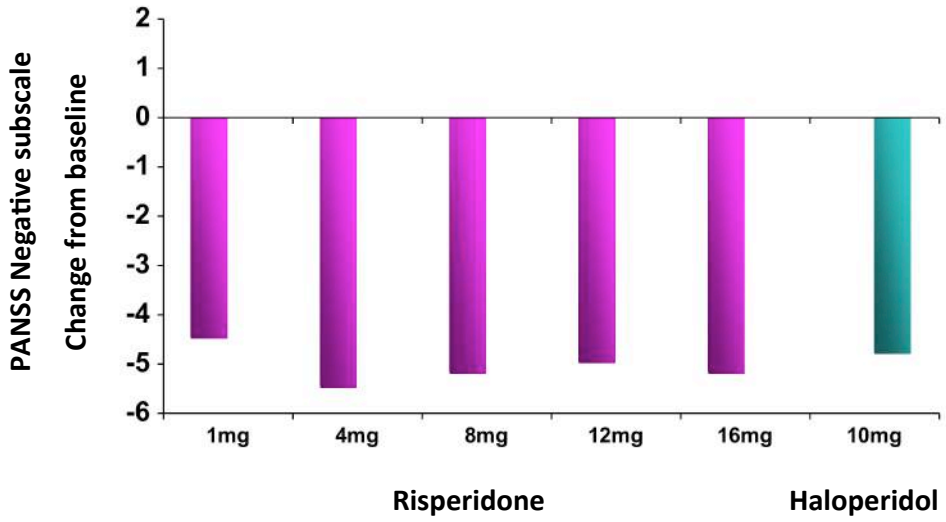
Velligan et al 1997; Green et al 2000; Bryson & Bell 2003; McGurk et al 2004

Figure 2: SGA versus FGA - efficacy in various domains Leucht et al. Lancet 2009



SMD = Hedges's g, N = number of studies, n = number of participants, SGA = second generation antipsychotic. Note that the results are significant if the confidence interval does not overlap with the x-axis.

PANSS Negative symptoms: Change from baseline

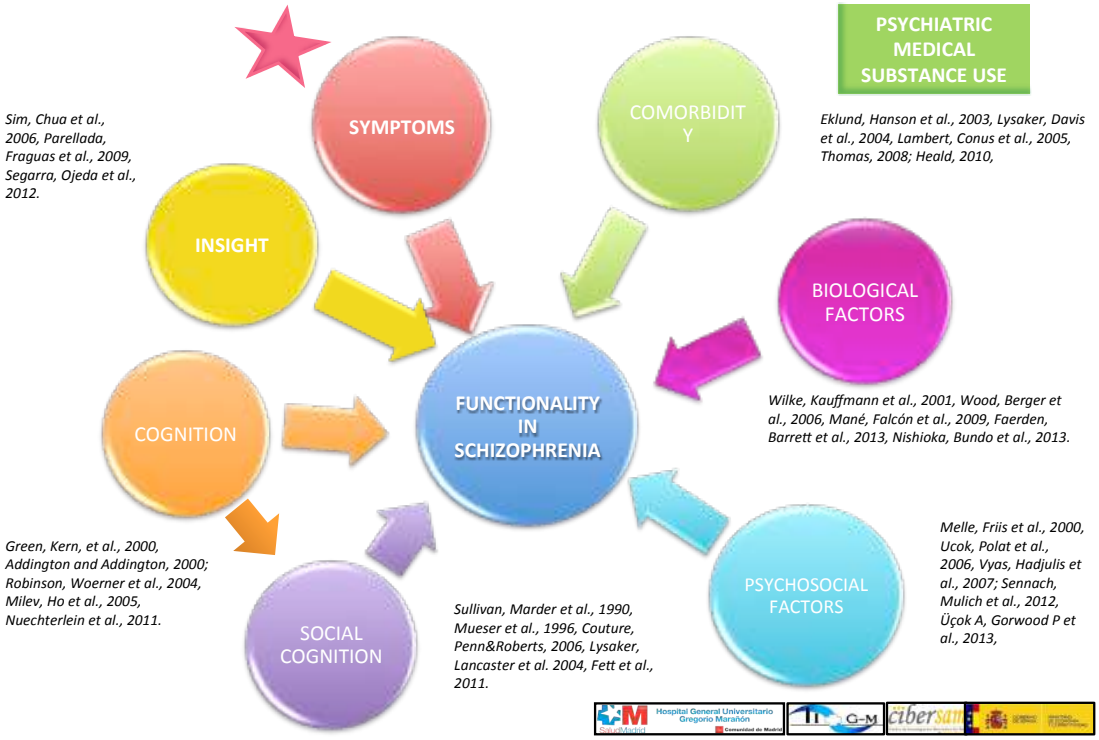


Schizophrenia: more than positive symptoms

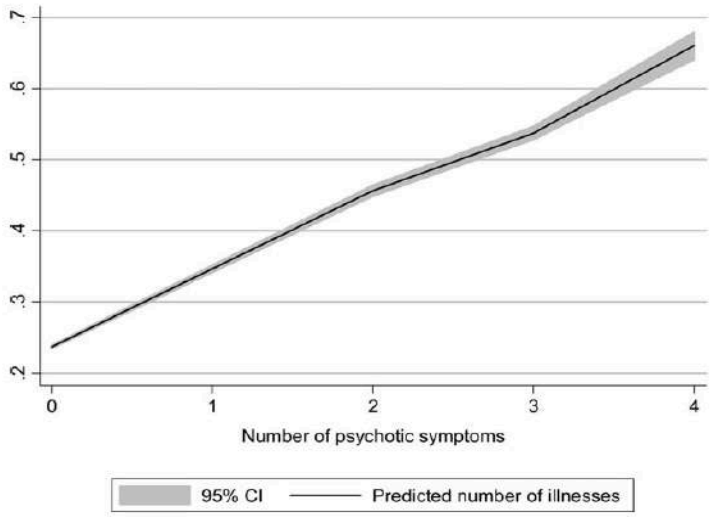
- **Positive symptoms** are the most easily recognised in the acute setting.
- But **negative and cognitive symptoms** need to be considered of:
  - Independent neurobiological substrate
  - greater influence on long-term functioning
  - increase the complexity of treatment
  - associated with a detrimental impact on patient self-care
  - increases family concern due to patient's lack of activity and limited occupational and social functioning

Carpenter et al 1988; Arango et al 2005; Meyer 2007; Rapado-Castro et al 2010

Functionality in schizophrenia

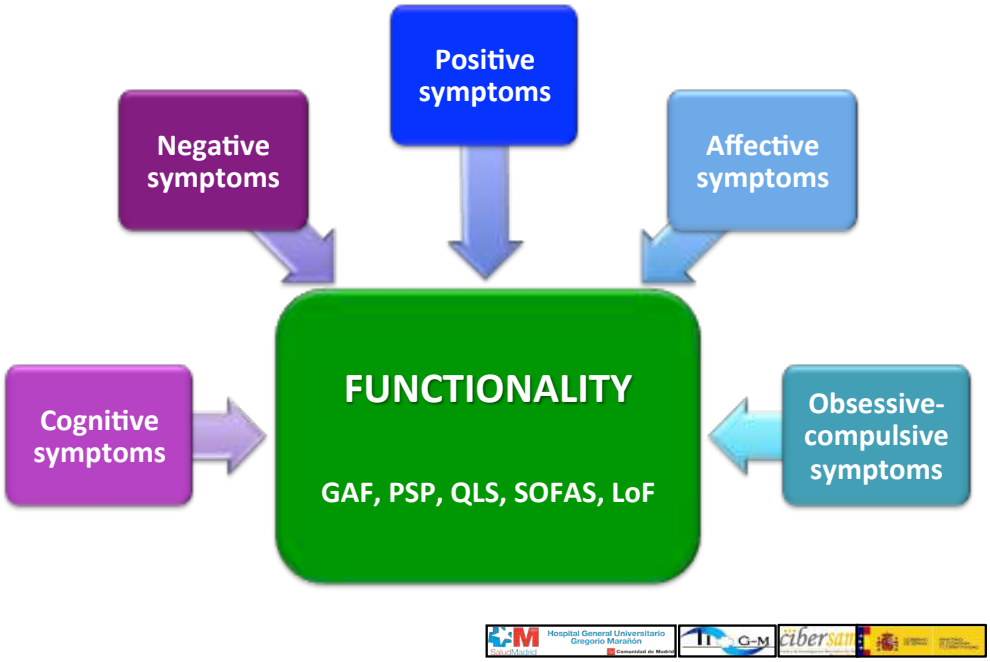


Number of medical comorbid conditions increases with number of psychotic symptoms



Moreno et al, 2013

Symptoms and functionality



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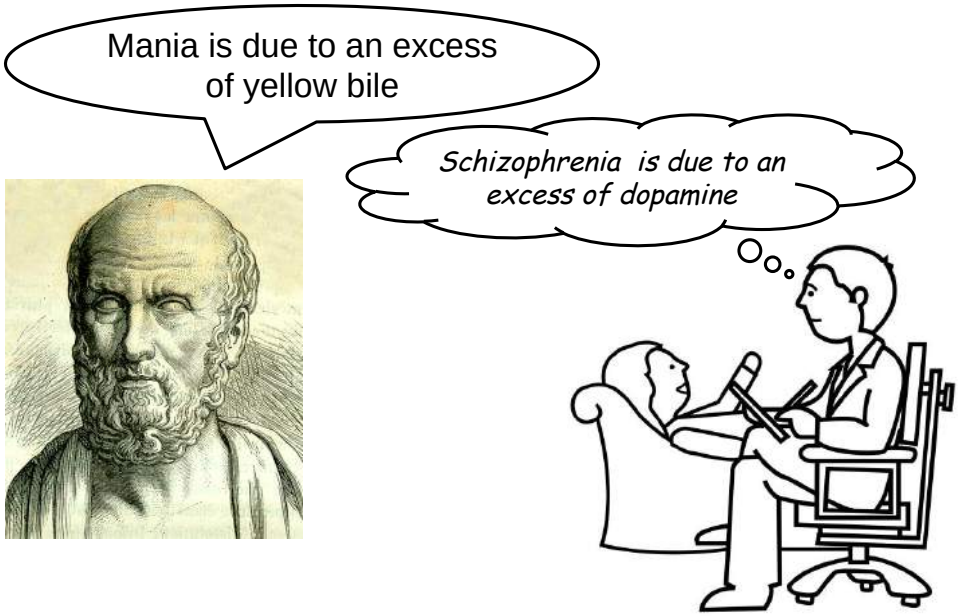
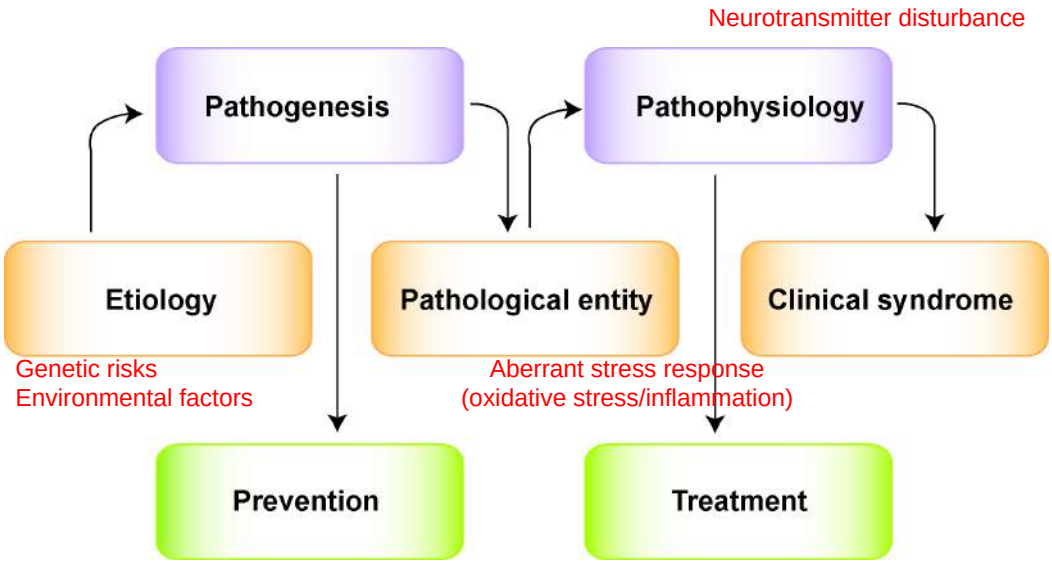
The past: great move ahead



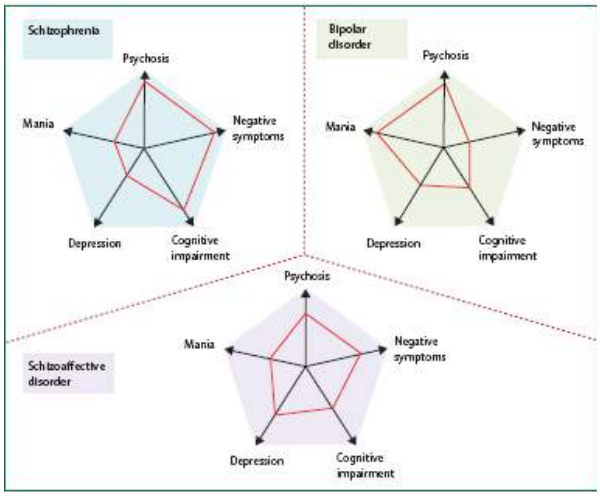
From etiologies to clinical phenotypes



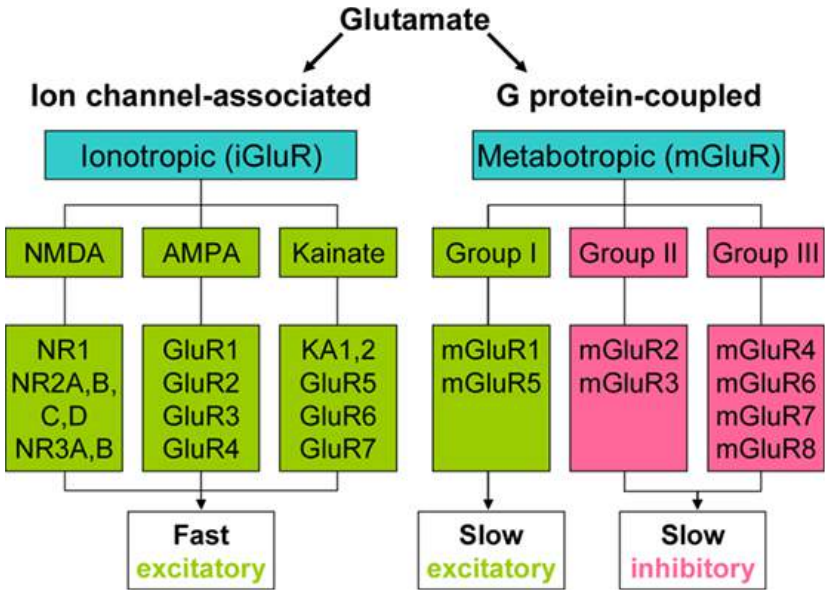
Paradigms for Therapeutic Discovery

1. Sz as disease
2. Sz as syndrome comprising disease entities
3. Sz as domains of psychopathology
4. Sz as impaired role and social function
5. Sz endophenotypes
6. Sz behavioral/neural circuit impairment
7. Sz development for primary prevention
8. Sz development for secondary prevention

Towards a dimensional model of psychosis and bipolar spectrum disorders



Dimensional model of psychosis
Van Os & Kapur, *Jama* 2009



Glutamatergic neurotransmission modulators under evaluation for schizophrenia treatment

NMDA receptor

Glycine site full agonists (glycine, D-serine, D-alanine)
Glycine site partial agonists (D-cycloserine)
Glycine type I transporter inhibitors (N-methylglycine, Bitopertin:negative studies, AMGEN: stopped)
D-serine transport inhibitors

AMPA receptor

Positive allosteric modulators (AMPAkines)

Metabotropic receptors

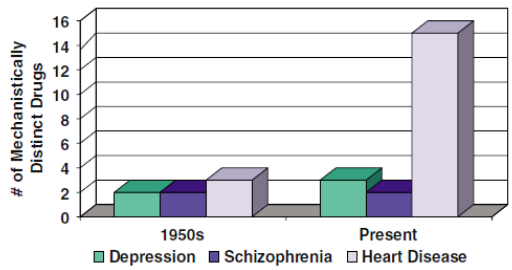
$mGluR_{2/3}$ activators (N-acetylcysteine)
$mGluR_{2/3}$ agonists (Pomaglumetad: failed)

Where should we put our effort in….

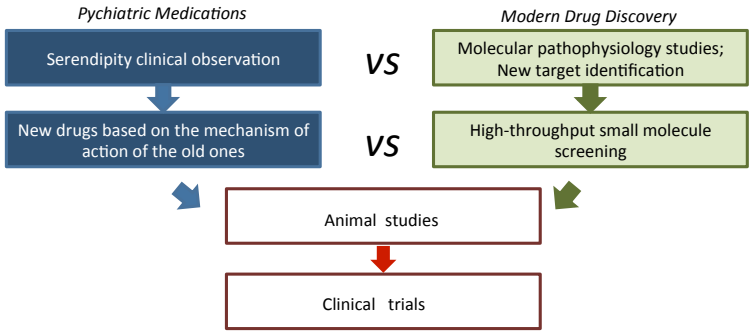
- Understanding the pathogenesis and mechanisms of psychopathology
- Targeting domains of brain function relevant to psychopathology across parallel units of analysis (genes, molecules, cells, circuits, behavior, etc.)
- Treatment development using experimental medicine methods:
  - Pathogenesis-derived target
  - Proof-of-concept studies for efficacy signal

33

New strategies for an old challenge: drug discovery in Mental Health

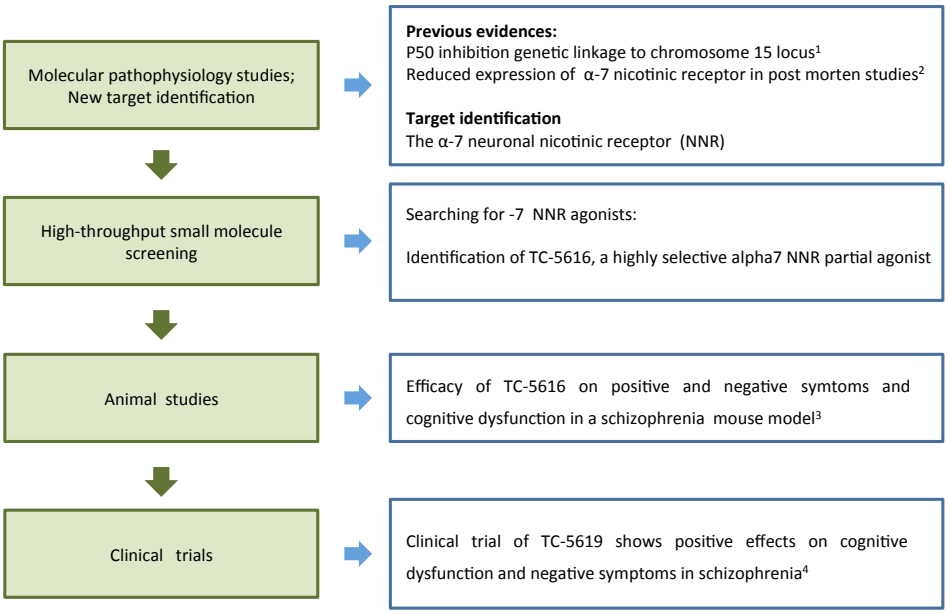


Are we doing something wrong?

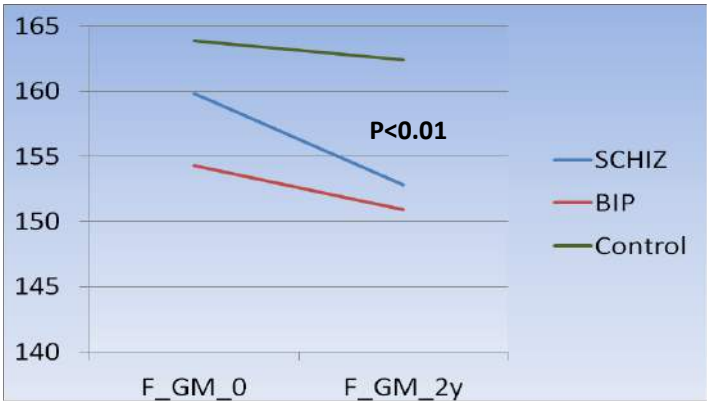


Insel T. R., Scolnick E. M. (2006). Mol. Psychiatry 11, 11–17

Modern drug discovery in mental health: The example



[1]Freedman R et al., PNAS 1997. [2]Freedman R et al., Biol Psychiatry 1995.
[3]Hauser TA., Biochem Pharmacol 2009. [4]Lieberman JA., Neuropsychopharmacology 2013



After 2 years of follow-up, children and adolescents with schizophrenia have:

-higher loss of gray matter volume in frontal lobe and

-higher CSF volume than controls

Arango et al., 2012

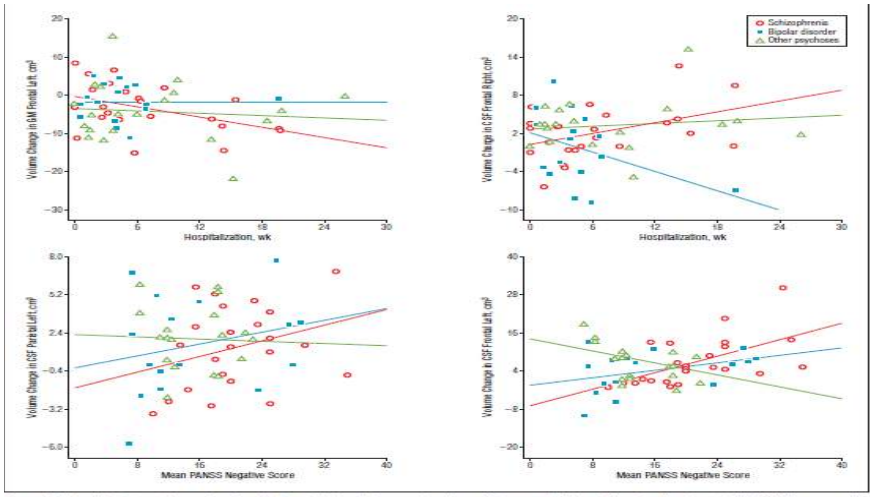


Figure. Relationship between the number of weeks hospitalized and the mean baseline and follow-up Positive and Negative Syndrome Scale (PANSS) score and gray matter (GM) and cerebrospinal fluid (CSF) volume changes within diagnostic subgroups.

Loss of GM volume correlated with markers of worse prognosis

-more weeks impatient
-less improveement in negative symptoms
-less improvement in PANSS total scores

Arango et al., 2012

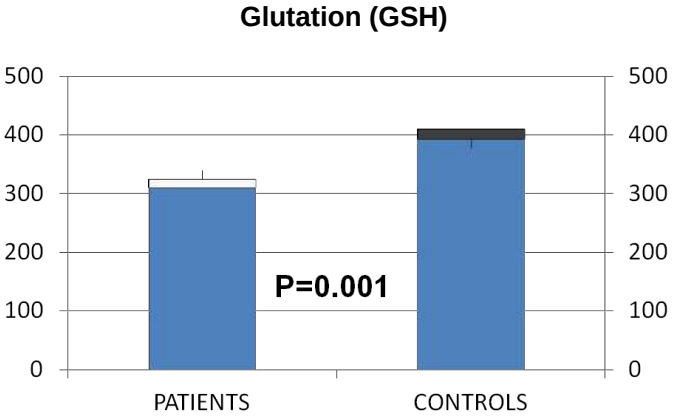
Decrease of GSH in psychosis vs controls

RESEARCH ARTICLE Open Access

Reduced antioxidant defense in early onset first-episode psychosis: a case-control study

Juan Antonio Micó[1], María Olga Rojas-Corrales[1], Juan Gibert-Rahola[1], Mara Parellada[2], Dolores Moreno[2], David Fraguas[3], Montserrat Graell[4], Javier Gil[5], Jon Irazusta[5], Josefina Castro-Fornieles[6], Cesar Soutullo[7], Celso Arango[2], Soraya Otero[8], Ana Navarro[9], Inmaculada Baeza[6], Mónica Martínez-Cengotitabengoa[9], Ana González-Pinto[1,9*]

May low GSH level contribute to grey matter loss?

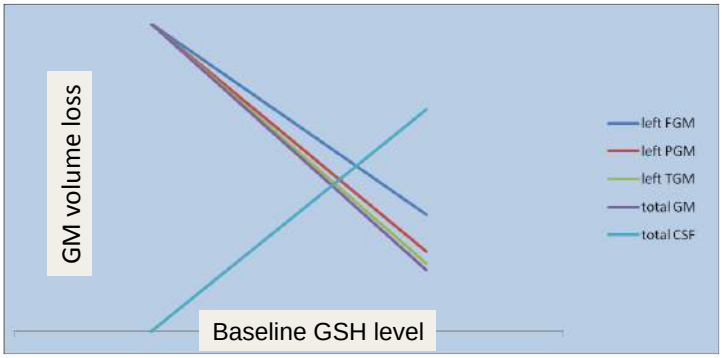


Micó et al. BMC Psychiatry 2011, 11:26
http://www.biomedcentral.com/1471-244X/11/26

Contents lists available at SciVerse ScienceDirect
Schizophrenia Research
journal homepage: www.elsevier.com/locate/schres

Decreased glutathione levels predict loss of brain volume in children and adolescents with first-episode psychosis in a two-year longitudinal study

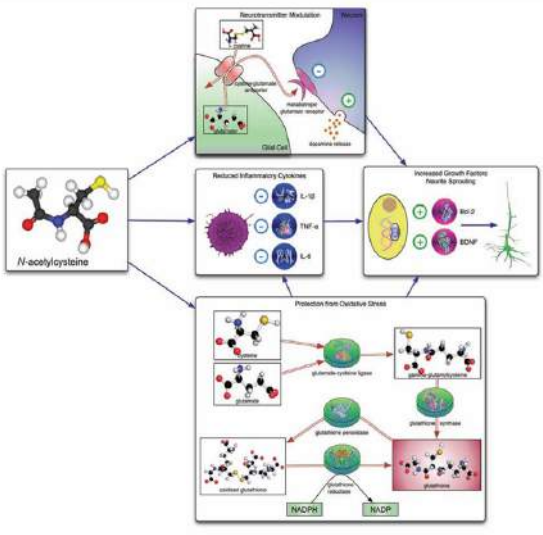
David Fraguas [a,b], Ana Gonzalez-Pinto [c], Juan Antonio Micó [d], Santiago Reig [a,e], Mara Parellada [a], Mónica Martínez-Cengotitabengoa [c], Josefina Castro-Fornieles [f], Marta Rapado-Castro [a], Immaculada Baeza [f], Joost Janssen [e], Manuel Desco [e,g], Juan Carlos Leza [h], Celso Arango [a,*]



Fraguas et al., Schizophrenia Research 2012

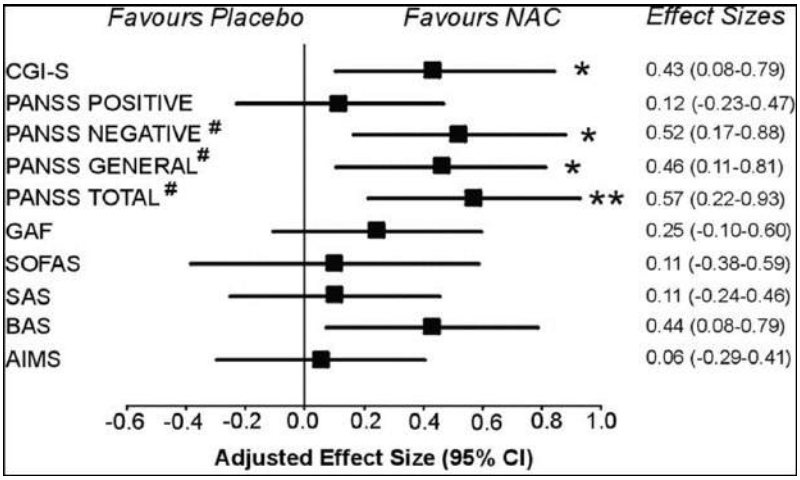
NAC: Mechanism of action

- Main GSH precursor
- Antioxidant
- Anti-inflammation
- Dopaminergic and glutamatergic modulation



Dean et al; J. Psychiatry Neurosci 2011; 36(2): 78-86

NAC, 2 g/d in schizophrenia



Berk M. et al., Biol. Psychiatry, 2008, 64: 361-368

Objetive

MAIN OBJECTIVE:

-To evaluate the effect of 48 weeks of N-Acetylcisteine on Grey Matter loss measured by MRI

Secondary objectives:

1. Effect on oxidative stress: central (MRS) and peripheral (TAOS, GSH/GSSG…).
2. Effect on white matter(DTI).
3. Psichopathology (PANSS, HAM-D, YMRS) y functioning (C-GAS, SOFAS).
4. Effect on antipsychotic dose and extrapiramidal symptoms (BARS, AIMS).

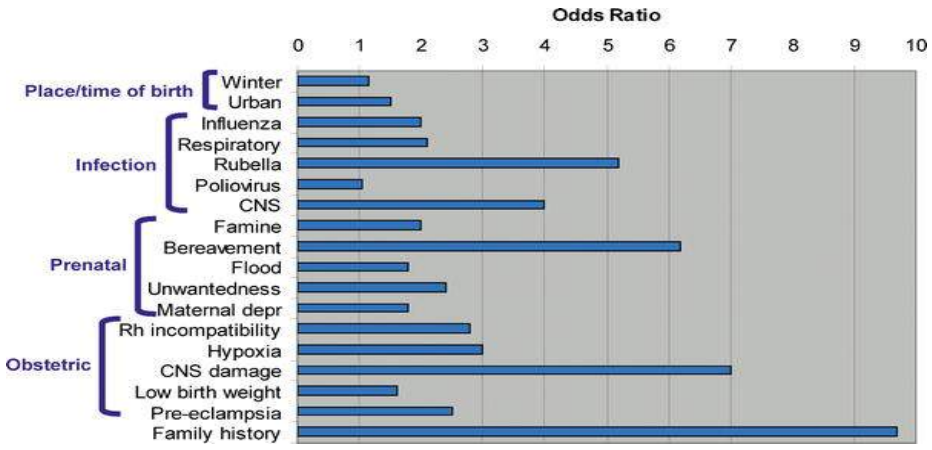
Studies	Country	No	Screening instrument	Age (yrs, range)	Comparison	Duration (wks)	Follow up (wks)
Addington 2011	Canada	51	Structured interview for prodromal symptoms	20.9 (NR)	CBT *vs* supportive counselling	26	52 and 78
Amminger 2010	Austria	81	PANSS	16.4 (NR)	Omega 3 fatty acids (1200 mg/day) *vs* placebo	12	52
Bechdolf 2012	Germany	128	Early Recognition Inventory	25.8 (NR)	Integrated therapies *vs* supportive counselling		04
McGlashan 2003	US	60	Structured interview for prodromal symptoms	17.8 (12–36)	Olanzapine (8 mg/da		
McGorry 2002	Australia	59	BPRS	20 (14–28)	Risp		156–208
McGorry 2013	Australia	115	CAARMS	17.6	and	52	52
Morrison 2004	UK	60	PA		d supportive counselling *vs* supportive counselling	52	156
Morrison 2012	UK			(14–34)	CBT and supportive counselling *vs* supportive counselling	26	104
Nordentoft 20				24.9 (NR)	Integrated therapies *vs* standard treatment	104	N/A
Phillips			CAARMS	17.9 (NR)	Risperidone (2 mg/day) and CBT *vs* CBT and placebo *vs* supportive counselling and placebo	52	104
Ruhrmann 2	Germany	124	Early Recognition Inventory	25.6 (NR)	Amisulpride (118.7 mg/day) and NBI *vs* NBI	12	N/A
Van der Gaag 2012	Netherlands	201	CAARMS	22.7 (NR)	CBT *vs* supportive counselling	26	52 and 78

Preventing transition to psychosis

NR, not reported; NBI, needs based intervention; CAARMS, Comprehensive Assessment of At Risk Mental States ; BPRS, Brief Psychiatric Rating Scale; CBT, cognitive behavioural therapy; PANSS, Positive and Negative Syndrome Scale; ICD-10, International Classification of Diseases

Stafford et al. *BMJ* 2013; Morrison et al. *BMJ* 2012; McGorry et al. *J Clin Psychiatry* 2013.

Many replicated risk factors for schizophrenia



PRIMARY PREVENTION?

Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, Leonard S, Stevens KE, Freedman R. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. Am J Psychiatry, 170(3):290-8, 2013.

Primary Prevention

Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, Leonard S, Stevens KE, Freedman R. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. Am J Psychiatry, 170(3):290-8, 2013.

CONCLUSIONS:
Neonatal developmental delay in inhibition is associated with attentional problems as the child matures. Perinatal choline activates timely development of cerebral inhibition, even in the presence of gene mutations that otherwise delay it.

Comment in: Rapoport JL. Prevention of schizophrenia: an impossible dream? Am J Psychiatry 170(3):245-7, 2013.

Concluding remarks

- Change the paradigm of D2 blockade
- Targeting mechanisms of action related to pathogenesis and mechanisms of psychopathology
- Primary prevention of vulnerability or treat disorder at vulnerability stage or secondary prevention of psychosis

KOEN SCHRUERS

NEW TREATMENT OPTIONS IN OCD

The lecture will cover the state of the art of treatments for OCD, covering both psychological and biological treatments. Special attention will be paid to the relatively novel option of deep brain stimulation. Several studies suggest that this is a promising technique, but many questions remain unanswered, for instance regarding the optimal target, the effect size and the long-term effects. The lecture will cover risks and benefits of this technique.

OCD

Phenomenology and Treatment

Focus on recent Developments

K.R.J. Schruers, MD PhD
Head Anxiety Disorders/OCD Program
Maastricht University

Obsessive-Compulsive Disorder

Obsessions:
Repeated, intrusive thoughts, images, impulses

Compulsions:
Repeated behaviour or thoughts
such as washing checking, or mental rituals

Prevalence

- Panic Disorder: 2-5%
- GAD: 2-5%
- Social Anxiety Disorder: 2-13%
- OCD: 2-3%
- PTSD: 1-7%
- Specific phobia: 5-11%
- Schizophrenia: 1.5%

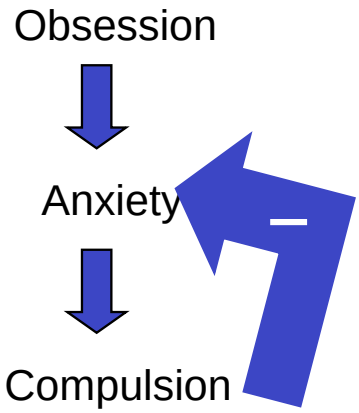
Comorbidity "Anxiety" Disorders

	Pure	1 Comorb	2 Comorb	+3 Comorb
OCD	32.4	31.5	13.4	23.0
PTSD	34.1	21.1	17.5	27.0
Sp. Fob.	63.2	26.8	6.6	3.4
Soc. Fob.	49.0	26.6	12.6	11.8
GAD	43.6	23.5	13.0	21.0
PD	24.6	36.7	13.3	23.5

Comorbidity with depression

	Current	lifetime	AD first	MD first
OCD	30%	70%	40%	10%
PTSD	35%	50%	?	?
Soc. Fob.		70%	70%	20%
GAD	?	60% (30%dyst)	55%	30%
PD	30%	60%	60%	20%

Obsessive-Compulsive Disorder

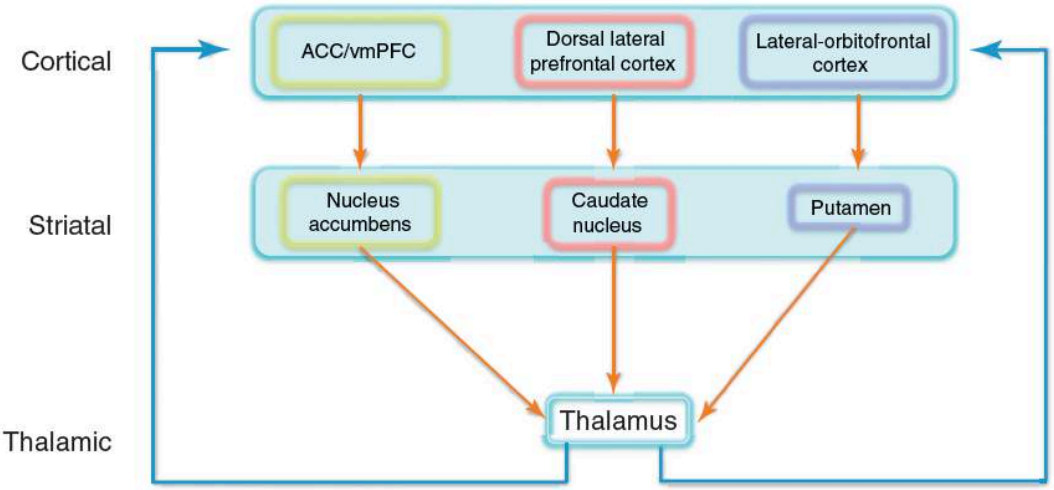


Frequency of Symptoms

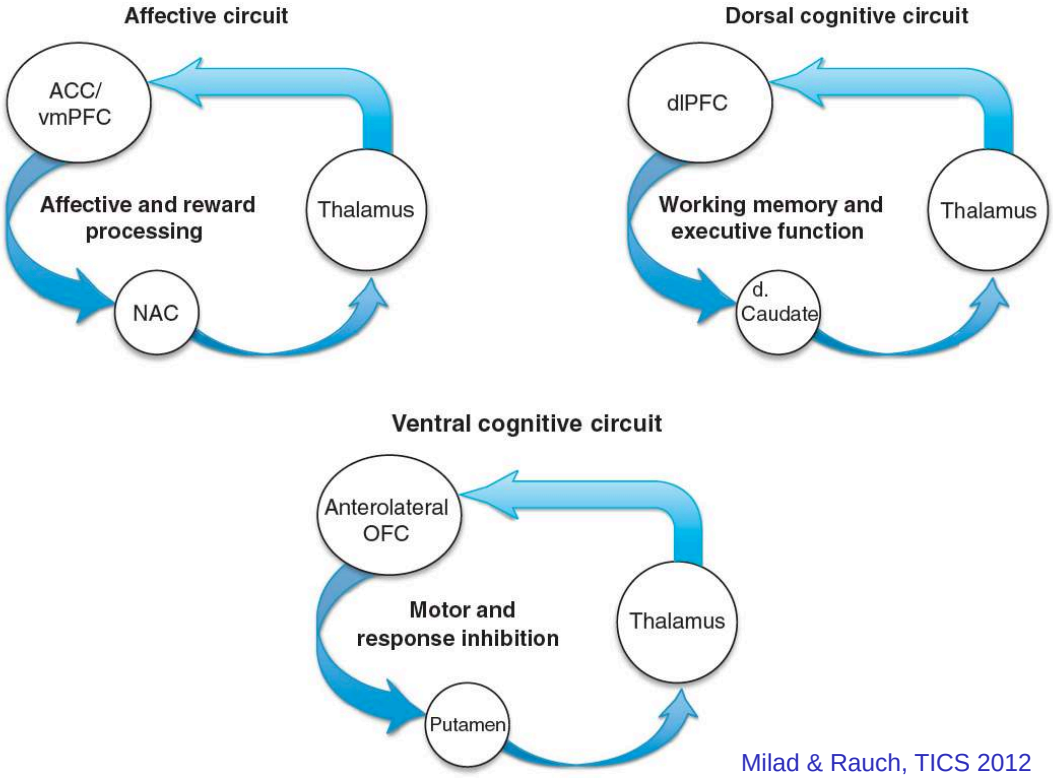
Obsessions	%
contamination	50
doubt	42
somatic	33
symmetry	32
aggressive	31
sexual	24
multiple	72

Compulsions	%
control	61
washing	50
counting	36
questioning	34
symmetry	28
hoarding	18
multiple	58

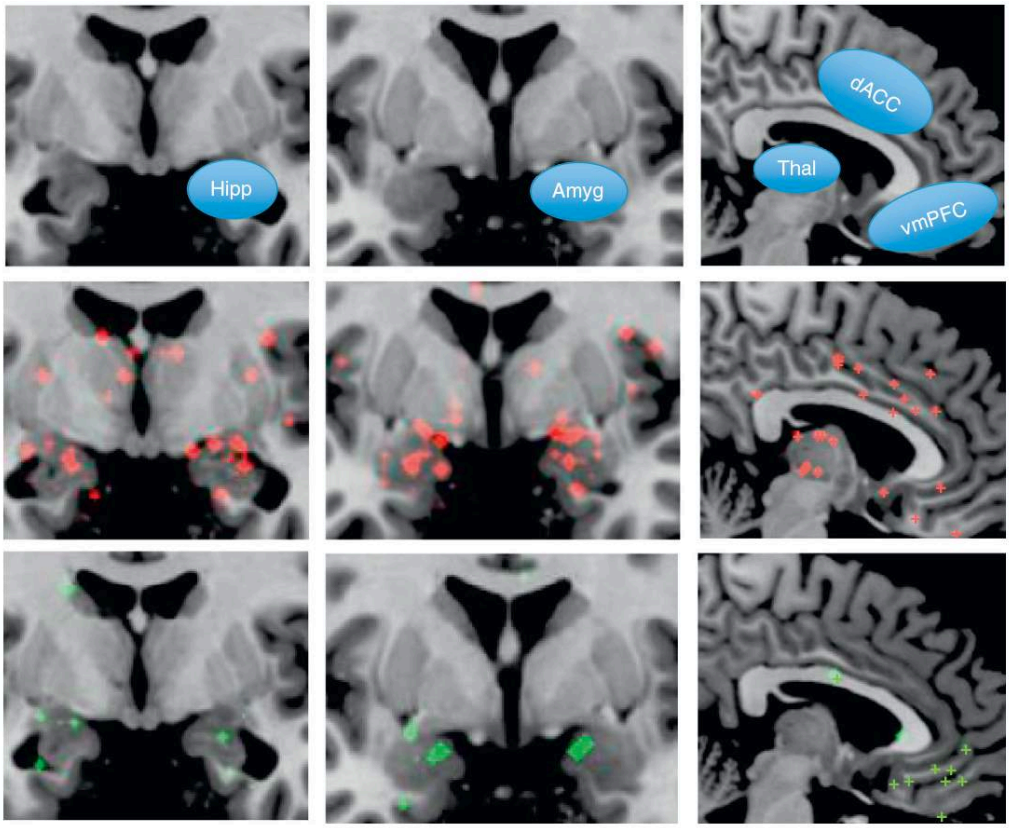
Neural circuitry



Milad & Rauch, TICS 2012



Milad & Rauch, TICS 2012



Treatment

CBT > Medication

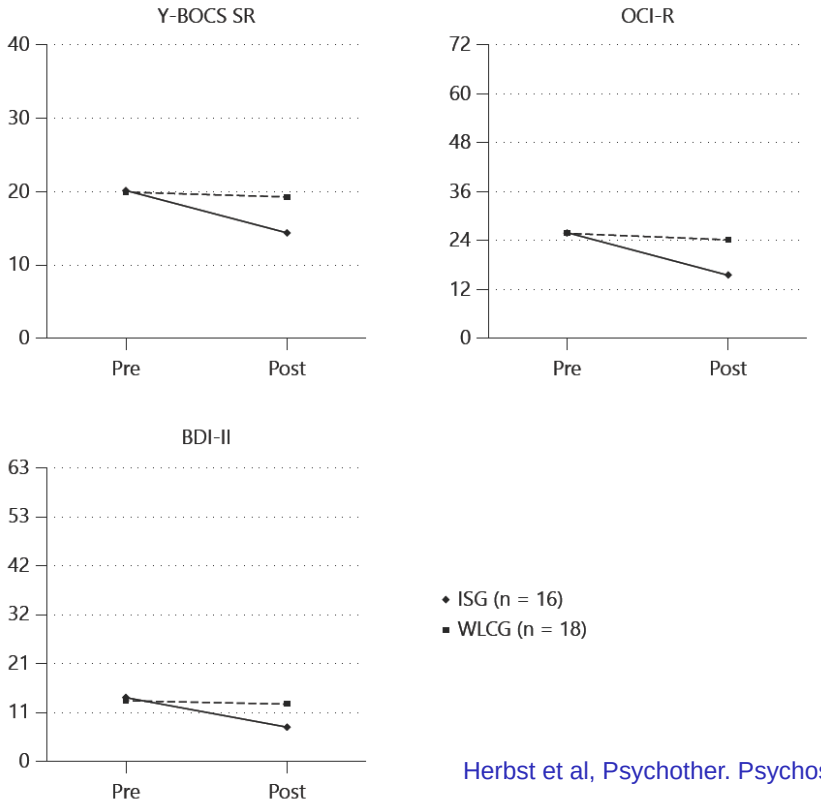
Combination

Behaviour therapy

- Exposure and response prevention
- Cognitive: Re-structurering of interpretations – Overestimate risk
  – Overestimate responsibility

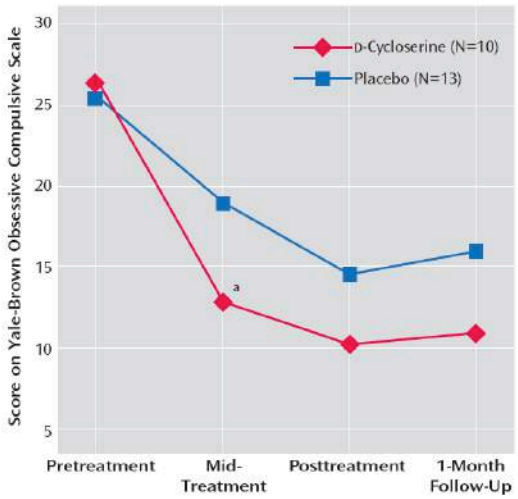
New Forms of Behaviour Therapy

- DCS Augmentation ?
- E-therapy ?
- VRET ?



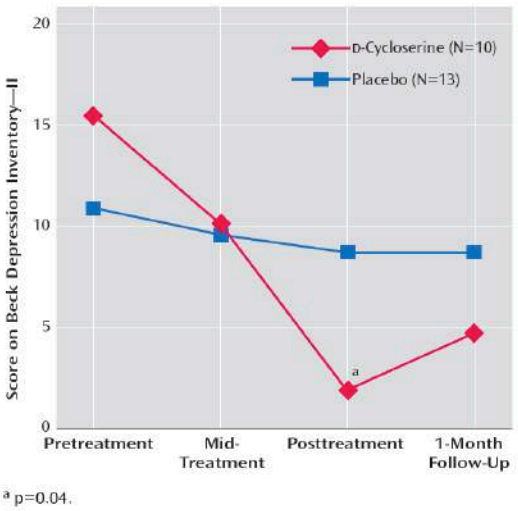
Herbst et al, Psychother. Psychosom. 2013

FIGURE 1. Decrease of Obsessive-Compulsive Disorder Symptoms Over the Course of Treatment



[a] p=0.009.

FIGURE 2. Decrease of Depressive Symptoms Over the Course of Treatment



[a] p=0.04.

Wilhelm et al, AJP 2008

First level pharmaco monotherapy

- Antidepressants:
  - SSRI's
    >
  - TCA's
- ~~Benzodiazepines~~
- ~~Neuroleptics~~

Pharmacological monotherapy for OCD: double blind, controlled studies

	Dose range (mg)	Effective	Reference
SSRIs			
Fluoxetine	20 --- 80	+	20 23, 38
Fluvoxamine	100 --- 300	+	18, 19, 39
Sertraline	50 --- 200	+	22, 25, 26, 28
Citalopram	20 --- 60	+	8
Paroxetine	20 --- 60	+	15, 24, 34, 35
SNRI			
Venlafaxine	300	+	34, 35
TCA			
Clomipramine	100 --- 300	+(+)	12 15, 38, 39

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant.

Schruers et al Acta Psych. Scand. 2005

SSRI's

	Start	Effective dosage	Effect (after reaching eff. dosage)	Duration (on eff. Dosage)
Citalopram	10 mg	20-60 mg	12w	1 year
Fluoxetine	10 mg	20-80 mg	12w	1 year
Fluvoxamine	50 mg	100-300mg	12w	1 year
Paroxetine	10 mg	20-60 mg	12w	1 year
Sertraline	25 mg	50-200 mg	12w	1 year
Escitalopram	10 mg	10-20mg	12w	1 year

SSRI's: Side Effects

- Short term:
  - Increased anxiety
  - Nausea
  - Head ache
  - Sleep disturbances
  - Sweating
- Long term:
  - Sexual dysfunction
  - Weight increase
  - (Sweating)

TCA's: Side Effects

- Short term:
  - Increased anxiety
  - Nausea
  - Drowsiness
  - Dry mouth
  - Blurred vision
  - Obstipation
  - Urinary retention
- Long term:
  - Sexual dysfunction
  - Weight increase
  - (Sweating)

CBT,SSRI or Combination?

- SSRI only: if no other option
- CBT alone: mild/moderate to severe OCD complaints
- Combination: - complicated
  - Long duration
  - Previous attempts
  - predominantly obsessions
  - comorbid depression

Medication: Augmentation

- Antipsychotics
- Fenfluramine
- Lithium
- Tryptophan
- Buspirone
- Trazodone
- Clonazepam
- Thyroid hormone
- Inositol

Drug (duration, wk)	Study	*n*	Dose, mg/d (mean dose)	Definition of clinical response: Response criteria	Response rate on active drug	Placebo response rate
Risperidone	McDougle *et al.* (2000)	36	1 titrated to 6 as tolerated (2.2)	Marked = 3 of a, c, e Partial = 2 of a, c, e	4/18 (22%) 5/18 (28%)	0/15 (0%)
Risperidone	Hollander *et al.* (2003)	16	0.5–3.0	–[b,d]	4/10 (40%)	0/6 (0%)
Risperidone	Li *et al.* (2005)	16	1	not defined	not reported	not reported
Olanzapine	Bystritsky *et al.* (2004)	26	up to 20 (11.2)	–[b]	6/13 (46%)	0/13 (0%)
Olanzapine	Shapira *et al.* (2004)	44	5–10 (6.1)	not defined	5/22 (23%)[a] 9/22 (41%)[b]	4/22 (18%)[a] 9/22 (41%)[b]
Quetiapine	Denys *et al.* (2004)	40	300	–[a,d]	8/20 (40%)	2/20 (10%)
Quetiapine	Carey *et al.* (2005)	41	300	–[b,d]	8/20 (40%)	10/21 (47%)
Quetiapine	Fineberg & Gale (2005)	21	400 (215)	–[b]	3/11 (27%)	1/10 (10%)
Quetiapine	Kordon *et al.* (2008)	40	400–600	–[a]	6/20 (33%)	3/20 (15%)
Aripiprazole	Muscatello *et al.* (2011)[f]	40	15	–[a,b]	4/16 (25%)[a] 11/16 (68.7%)[b]	0/14 (0%)

[a] ⩾35% improvement in Yale–Brown Obsessive Compulsive Scale (YBOCS).
[b] ⩾25% improvement in YBOCS.
[c] Final YBOCS score <16.
[d] CGI of "much improved" or "very much improved".
[e] Consensus opinion of investigators.
[f] Completer analysis.

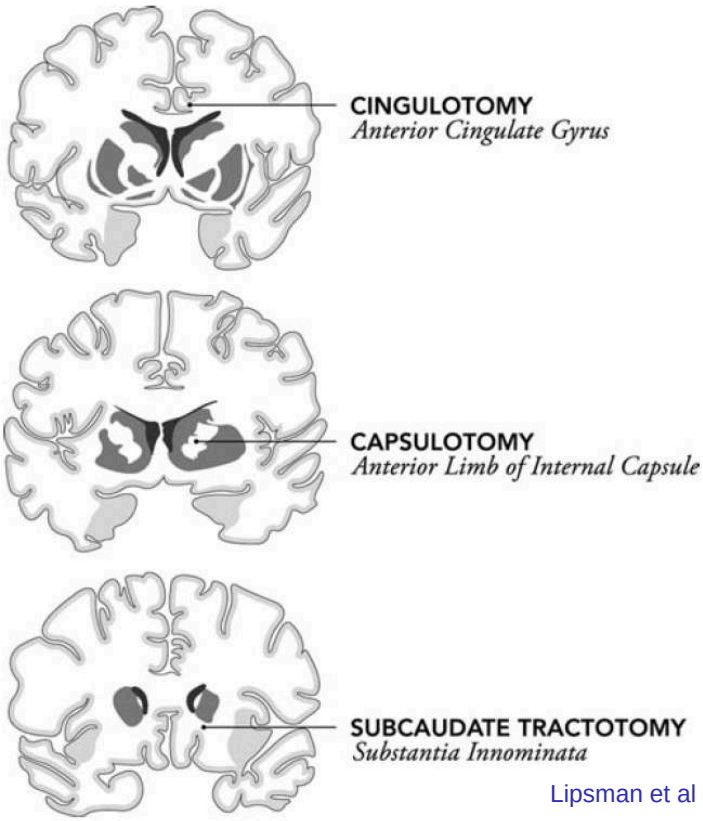
Fineberg et al, IJNP 2012

Electricity

- ~~ECT~~
- rTMS ???
- Lesion surgery
- DBS

Lesion neurosurgery

- Cingulotomy
- Capsulotomy
- Subcaudate tractotomy
- Limbic leucotomy



Lipsman et al Neurosurg 2007

Lesion neurosurgery: risks

- Infection
- Bleeding
- Epilepsy
- Delirium
- Neuropsychological dysfunction
- Personality changes

Irreversible

Lesion Neurosurgery: effect

- Many older studies: 50-67% success rate

- Not blind
- Selection bias
- No reliable outcome measures
- No evaluation of personality

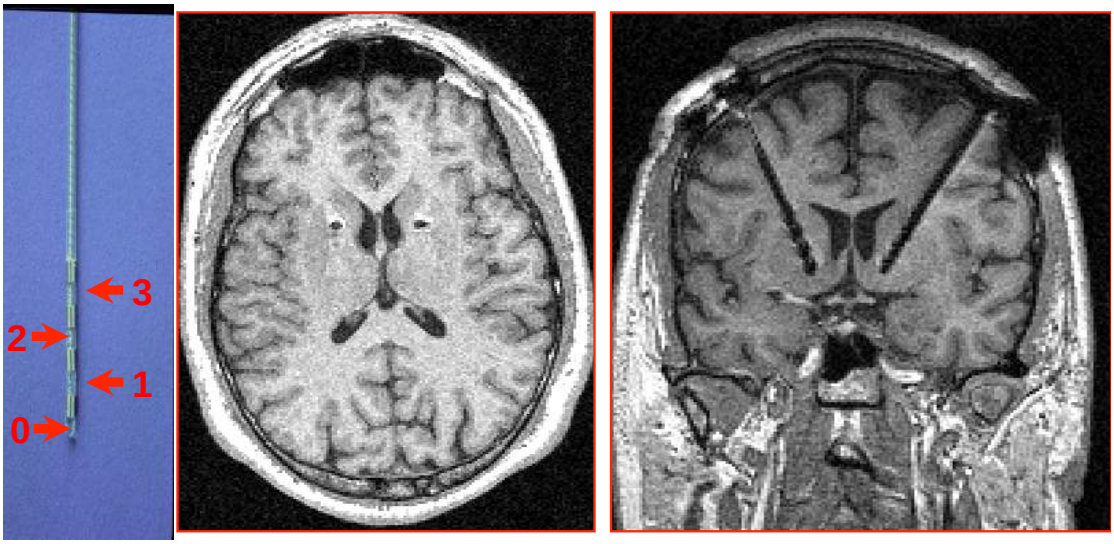
- Recent studies: 25-32% success rate

Deep Brain Stimulation

- Electrical stimulation
- Pacemaker

- Crus anterius capsula interna
- Nucleus accumbens
- Nucleus subthalamicus
- Inferior thalamic pedunculus

Target: crus anterius of the internal capsules



Nuttin B, Gabriëls LA, Cosyns PR, et al. Long-term Electrical Capsular Stimulation in Patients with Obsessive-Compulsive Disorder. Neurosurgery 2003;52(6):1263-1274.

Table 2. Patient Characteristics in Reports of ≥5 Individual Patients with Deep Brain Stimulation for Obsessive-Compulsive Disorder

	Greenberg et al., 2008 (25)	Huff et al., 2010 (32)	Denys et al., 2010 (17)	Mallet et al., 2008 (42)	Jiménez-Ponce et al., 2010 (33)
Target	VC/VS	Unilateral right NA	NA bilateral	STN	ITP
Coordinates	Gradually changed from 15 mm anterior of AC to within 1 to 2 mm of the posterior border of the AC, further somewhat more medially and more inferior to include most often the caudal NA	Visual targeting based on the IC and the band of Broca	3 mm anterior of the anterior border of AC, laterality 7 mm, 4 mm inferior of ICL	"2 mm anterior to and 1 mm medial to the target that is used in patients with Parkinson's disease"	3.5 mm lateral to the wall of the 3rd ventricle, 5 mm behind the AC, at the AC-PC-plane
Number of patients	26	10	16	16	5
Male/female	14/12	6/4	9/7	9/7	3/2
Age at onset (years)	15.1		14.2		
Duration (years)	22	22.2	28.4		17
Age at surgery (years)	37.1	36.3	42.6	43.8	37
Evaluation presented here	Last follow-up, after a mean 24 months	12 months	12 months	3 months of active stimulation	12 months
YBOCS preoperative/postoperative	34.0/~21	32.2/25.4	33.7/17.8	32.1/19	35/17.8
HDRS preoperative/postoperative	52.8% reduction	HDRS: 21.6/16.6	HDRS-17: 19.5/10.3		
HAMA preoperative/postoperative	50.0% reduction	21.2/15.0	20.9/9.7		
GAF preoperative/postoperative	34.8/59.0	36.6/53.1		31.6/56	18/72
SDSS preoperative/1 year			8.6/4.8		
Stimulation parameters		Monopolar, 2 to 3 contacts, 4.5 to 6.5 V, 90 to 140 μS, 145 Hz	Monopolar, 2 contacts, 3.5 to 5 V (mean 4.3), 90 μS, 130 Hz	27 electrodes monopolar, 2 bipolar, 2.0 V	Bipolar, 5.0 V, 450 μS, 130 Hz
Number of responders	61.5%	1/10	9/16		

When multiple publications exist regarding the same patients, only 1 has been included here. DBS, deep brain stimulation; OCD, obsessive-compulsive disorder; VC/VS, ventral internal capsule/ventral striatum; NA, nucleus accumbens; STN, subthalamic nucleus; ITP, inferior thalamic peduncle; AC, anterior commissure; IC, internal capsule; ICL, intercommissural line; PC, posterior commissure; YBOCS, Yale-Brown Obsessive Compulsive Scale; HDRS, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Scale; GAF, Global Assessment of Function Scale; SDSS, Sheehan Disability Scale score.

Blomstedt et al World Neurosurg 2013

Deep Brain Stimulation

- Reversible

- Infection
- Bleeding
- …

- Still limited data !!

Team DBS OCD Maastricht

- Yasin Temel, Linda Ackermans: neurochirurgen

- Annelien Duits: neuropsycholoog

- Koen Schruers, Albert Leentjens: psychiaters

DINA POPOVIC

STRATIFIED TREATMENT OF BIPOLAR DISORDER

Maintenance therapy is a critical part of treatment of Bipolar Disorder. Clinical practice requires deciding upon the most appropriate treatment for each patient, which is often challenging.
Stratification of treatments for bipolar disorders based on biomarkers and improved clinical markers are greatly needed to increase the efficacy of currently available treatments and improve the chances of developing novel therapeutic approaches.
During this presentation, the most promising markers for stratification regarding treatment efficacy will be presented and the available evidence on how to choose the most effective treatment for each patient with bipolar disorder, in the era of individualized medicine, will be critically examined.

Bipolar Disorder Relapse Rates:

- 40%-60% after I lifetime episode

~50% of patients experience II mood episode within a year of recovery[1]

Inadequate treatment

↑ Relapse rates [2]

↑ Vulnerability to utter episodes[6]

↓ Response to Therapy [1]

↓Psychosocial Functioning[3,4]

↑Morbidity and mortality[5]

[1]Tohen,2006; [2]Prien, 1973; [3]Martinez-Aran, 2007, [4] Angst, 2002; [5] Suppes, 2009; [6]Ketter, 2006

Relapse prevention is a critical objective of treatment in bipolar disorder

- Evidence of ability to reduce risk of relapse is an important consideration in choice of maintenance therapy[1]

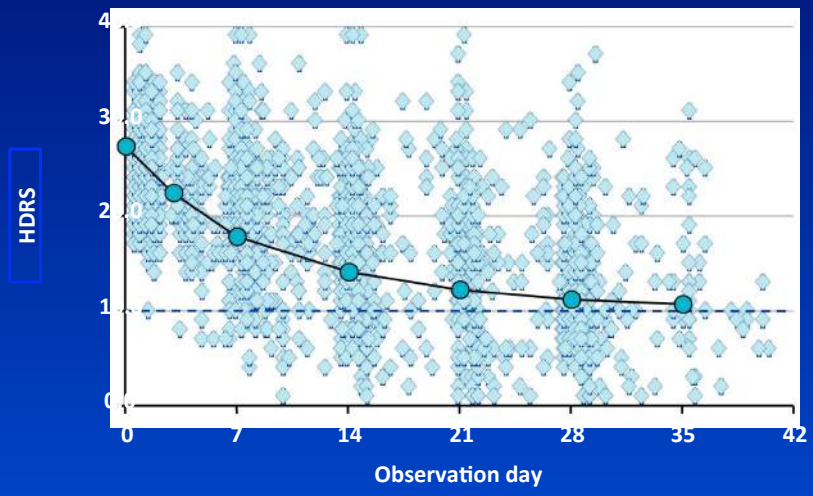
➢ **What?**

➢ **To whom?**

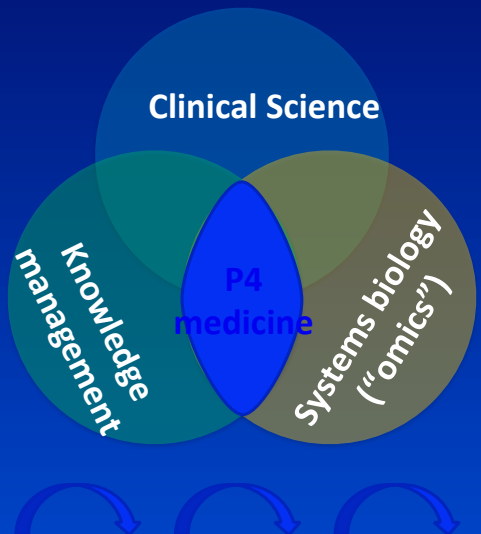
➢ **Why (Effectiveness)?**

1 Goodwin et al., 2009

Clinical trials show mean values, not individual data



PERSONALIZED MEDICINE



"Coupling established clinical-pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient's requirements"

NEJM 2012; January 19

Personalized; Predictive; Preventive; Participatory: Precision Medicine

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Personalized management of bipolar disorder

STRATIFYING BY:

- Psychopathological markers
- Genetics
- Epigenetics
- Endophenotypes: neuropsychology (neurocognition) neuroimaging; neuroeconomy
- Staging (life-span staging; functional staging
- Stratifying by predominant polarity
- Stratifying by comorbidity
- Stratifying by mixed features

Vieta 2014; Hasler and Wolf, 2015; Schumann et al, 2013

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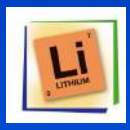
Clinical markers of response to Lithium

- Episodic clinical course with complete interepisodic remission. Mania-depression pattern
- Low comorbidity
- No rapid cycling
- Better efficacy in euphoric vs. dysphoric mania
- Bipolar family history with similar course of illness in the offsprings

Grof, 2010; Perugi et al., 2001; Vieta et al., 2005; Kleindienst, 2005; Rybakowski, 2013

Clinical markers of response to Lithium

- Later age at onset
- Low hospitalization rate
- Hyperthymic personality (Negative correlation with cyclothymic and anxious temperament)
- Preservation of cognitive functions and lack of cognitive disorganization



Rybakowski, 2012, 2013

Clinical factors of response to Carbamazepine

- CBZ> LI
  - psychiatric comorbidity
  - -mood-incongruent delusions
  - -EEG pathology, structural brain changes
- Bipolar I: Li >CBZ
- Bipolar II: Li = CBZ

Clinical factors of response to Valproate

- Atypical features ?
- More manic or mixed episodes VPA>LI

Kleindienst and Greil, 2000; Zarate et al.,1995: Rybakowsky et al., 2013

Clinical factors of response to Lamotrigine

- Chronicity of course, rapid cycling
- Comorbidity with anxiety disorders (panic disorder) and substance abuse
- Family history of schizoaffective disorder, recurrent depression, panic disorder

Clinical factors of response to Clozapine

- Severe manic episodes with psychomotor agitation and psychotic symptoms of great intensity

Passmore, 2003: Zarate et al., 1995

Clinical markers related with response to treatment:state specifiers

- Mixed episode: Olanzapine, Asenapine[1,2]
- Agitation (in mania): Asenapine, loxapine, aripiprazole[3-7]
- High suicidal risk: lithium[7]

Grunze&Azorin 2014 (1); Kruger 2005 (2); Brown,2013 (3); Gonzalez 2013 (4); Kwentus 2012 (5); McIntyre 2009 (6); Popovic (in press); Baldessarini 2006 (7)

Biological markers of lithium response

- Genes identified by candidate gene studies:
  - Neurotransmitters (5HTTLPR, DRD1)
  - Intracellular signaling (INPP, CREB1)
  - Neuroprotection (BDNF)
  - Other (BCR, CACNG2)
- Genes related to impulsivity and suicide risk: IMPA1, IMPA2, INPP1,GSK3 (alpha and beta)
- Genes identified by GWAS studies:
  - *GRIA2, ACCN1, SLCA410*

Rybakowski, 2013; Jimenez 2013

Stratification of therapies based on genetics

- **GRIA2**- role in lithium effect
- **XBP1** (cellular reactions to stress)- predictor of response to VPA
- **BDNF** Met allele of rs6265- response to lithium, brain aging and chronification of psychiatric disorders
- Polymorphism of SER transporter gene and the gene for SER receptor 5HT1A have potential to assess the AD effect

Hasler and Wolf,in press; Perlis,2009;

Stratification based on epigenetics

- Preliminary findings that cerebral epigenetic inhibition of GABAergic gene expression is involved in development of BD (low expression of GAD67,which sinthesizes GABA, with inhibition of GABA system)
- VPA inhibits various hystone deacetylases; specifically encourages GAD67 expression
- Clozapine and sulpiride promote DNA methylation as well
- Most epigenetic changes are specific for cells and tissues

Hasler and Wolf,in press; Guidotti,2011; Dong 2008,2010

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Stratification based on endophenotypic markers

- Intermediate phenotypes standing between genes and gene products and clinical syndrome
- Can be cathegorized according to a gradient between genes and clinical symptoms (i.e. neuropsychological endophenotypes vs. MRS-determined concentration of neurotransmitters)
- Endophenotypes could help tailor psychiatric diagnostics, therapy and prevention(?) to pathological processes

Hasler and Wolf, 2015

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Stratifying by functional imaging

- Heterogeneous findings, small samples, low consistency of findings
- Increased activity of subcortical,limbic regions, with reduced activity of the lateral prefrontal cortex- in mood and anxiety disorders
- Not relevant for stratified medicine unless it can be linked to treatment
- ADs efficacious in mood disorders in patients with limbic hyperactivity
- Deep brain stimulation efficacious in patients with limbic hyperactivity in BD and unipolar depression

Hasler and Wolf, in press;
Delvecchio, 2012; Chen,2007; Mayberg,1997;
Hotzheimer, 2012

Stratifying by structural imaging

- Main findings:

  1) Abnormal volume of the anterior cingulate and decreased integrity of white matter- risk for BD
  2) Regional brain volume decreases in BD
  3) LI-treated patients exibit larger brain volumes
  4)White matter atrophyc alterations in BD

- Evidence that excessive corticosteroids, glutamate neurotoxicity, mytochondrial disfunction and stress-induced decrease of neurotrophic factors lead to decrease in gray matter

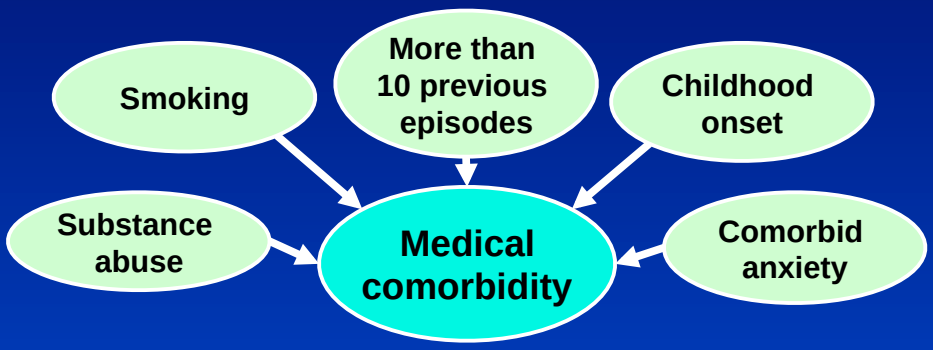
Hasler and Wolf, in press; Ahn,2004; Aylward 1994; Beyer 2009; Marlinge 2014; Munakata 2005; Nugent 2006; Sneyder 2011, Stork and Renshaw 2005

Structural imaging and stratified medicine

- Response to ADs correlates + with gray matter volume of the anterior cingulate, insula and right temporoparietal cortex, ADs may be more efficacious in the early stages of BD
- Neuroprotective drugs (i.e. LI and VPA) may positively interact with neurotrophic processes underlying the clinical simptoms

Hasler and Wolf, in press; Chen 2007; Chiu

Factors associated with medical comorbidity in bipolar disorder (STEP-BD)



Medical comorbidity is a core feature of bipolar disorder associated with greater illness chronicity, burden and worse outcomes

Magalhães et al 2012

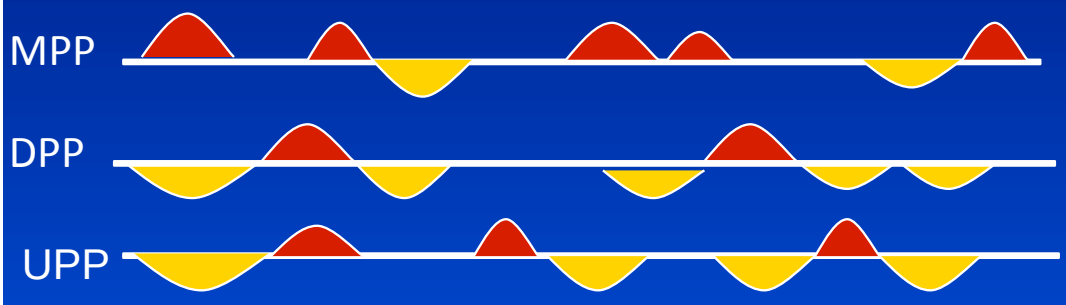
Clinical staging in bipolar disorder

Stage	Clinical features
Latent	• At risk for developing bipolar disorder (positive family history, abuse, substance abuse) • No specific symptoms
I	• IA: mild or non-specific symptoms or mood disorders • IB: prodromal features
II	• First episode threshold mood disorder
III	• Recurrence of sub-threshold mood symptoms • Multiple relapses
IV	• Unable to live autonomously due to cognitive and functional impairment

Berk et al 2007; Kapczinski et al 2009

Stratifying according to the Predominant Polarity

≥2/3 of a patient's past episodes fulfilling DSM-IV criteria for Depression or Mania/ Hypomania



MPP=Manic predominant polarity
DPP=Depressive predominant polarity
UPP=Undetermined predominant polarity

Colom et al., JAD, 2006

Predominant Polarity

~50% (45-70%) Predominant Polarity

Manic Polarity

- 40% (>50% in Israel)
- Manic Onset

Depressive Polarity

- 50-60%
- Depressive Onset
- BD II
- More years undiagnosed

Colom, 2006; Tohen, 2009; Osher,2000

Maintenance treatment choice: pharmacologic considerations

- Efficacy: NNT
- Safety : NNH
- Tolerability

} ***EFFECTIVENESS***

- Efficacy for each pole: Polarity Index
- Combination of drugs
  - Efficacy – sinergic actions
  - Safety/tolerability

Efficacy: Number Needed To Treat (NNT)

A measure of effect size that quantifies the clinical relevance of a study result

$$NNT = \frac{1}{\text{Response Rate Drug} - \text{Response Rate Placebo}}$$

NNT	d	Effect size
3	0.8	"Large"
4	0.5	"Medium"
9	0.2	"Small"

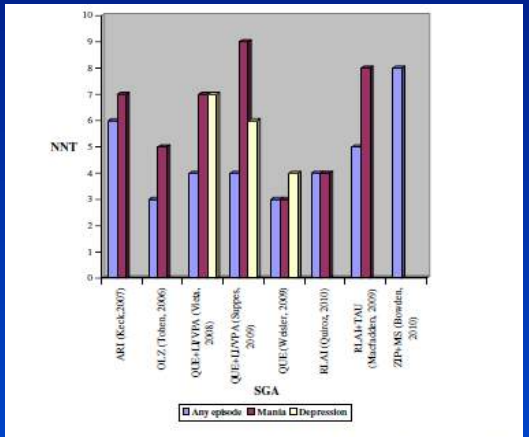
- The smaller the NNT, the more effective the treatment is!!
- NNTs <10 are considered clinically meaningful

Psychopharmacology (2011) 213:657–667
DOI 10.1007/s00213-010-2056-8

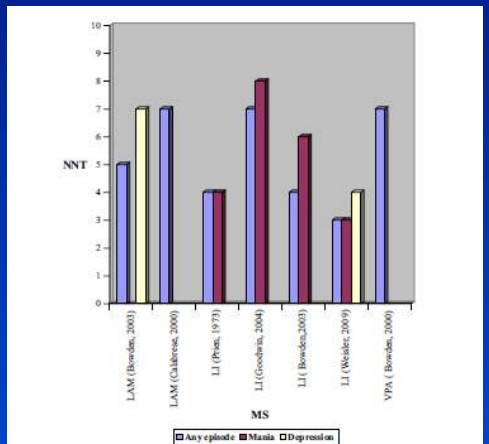
REVIEW

Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder

Dina Popovic · Maria Reinares · Benedikt Amann · Manel Salamero · Eduard Vieta



SGA= second generation antipsychotic, MS= mood stabilizer, PLA=placebo, ARI= aripiprazole, OLZ= olanzapine, LI=lithium, VPA= valproate, QUE=quetiapine, RLAI= risperidone long acting injection, TAU= treatment as usual, ZIP=ziprasidone



SGA= second generation antipsychotic, MS= mood stabilizer, PLA=placebo, LI=lithium, VPA= valproate, LAM=lamotrigine


European Neuropsychopharmacology (2012) 22, 339–346

www.elsevier.com/locate/euroneuro

Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder

Dina Popovic [a,b], Maria Reinares [a], Jose Manuel Goikolea [a], Caterina Mar Bonnin [a], Ana Gonzalez-Pinto [c], Eduard Vieta [a,*]

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[c] Santiago Apóstol Hospital, University of the Basque Country, CIBERSAM, Vitoria, Spain

A measure of the relative prophylactic efficacy of drugs used in bipolar disorder maintenance treatment

$$\text{Polarity Index} = \frac{\text{NNT depression}}{\text{NNT mania}}$$

PI = 1

Predominantly Antidepressive PI | Predominantly Antimanic PI

Polarity Index of medicaments used in maintenance treatment of BD

PI = 1

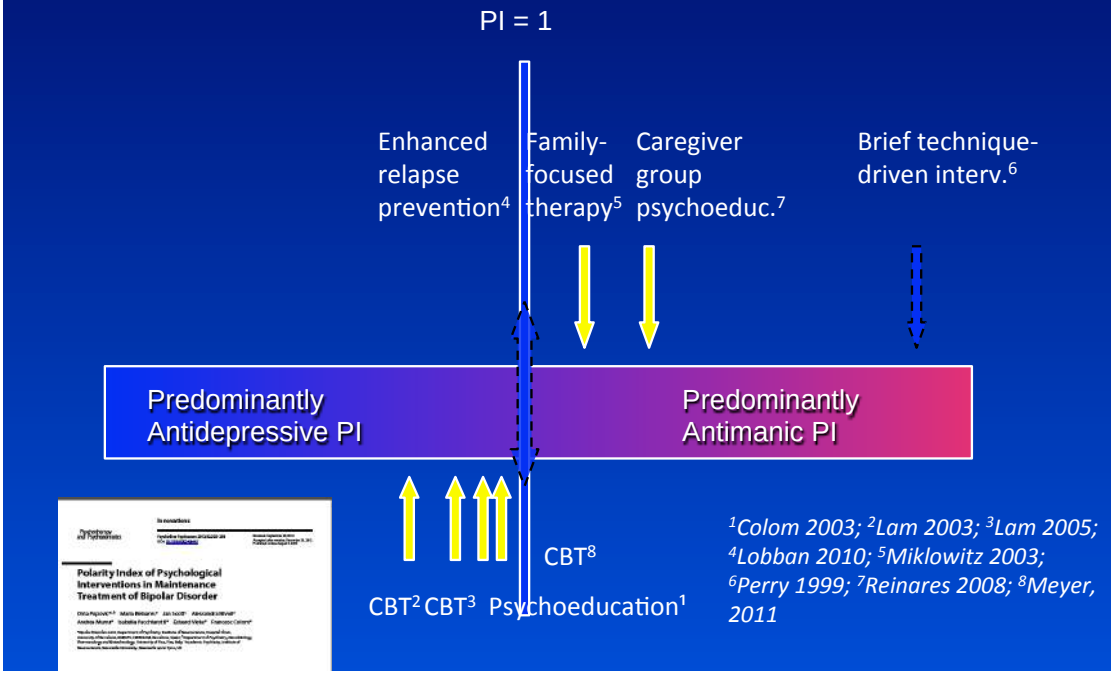
QUE 1.14 | LI 1.39 | OLZ2.98 | ZIP 3.91 | ARI 4.38 | RLAI 12.09

Predominantly Antidepressive PI | Predominantly Antimanic PI

LAM 0.40 | VPA 0.49 | XC 0.62

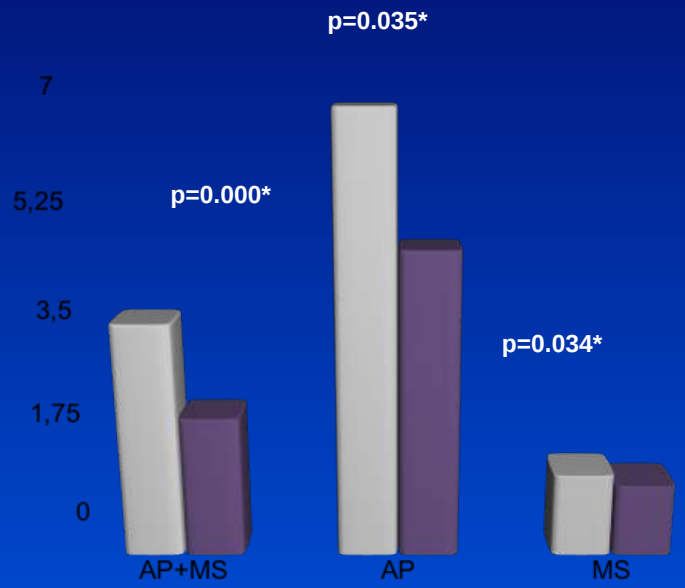

Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder

Polarity Index for Adjunctive Psychotherapies in maintenance treatment of BD



Polarity Index of Psychological Interventions in Maintenance Treatment of Bipolar Disorder

Polarity Index in maintenance treatment of BD




Acta Psychiatrica Scandinavica
Clinical implications of predominant polarity and the polarity index in bipolar disorder: a naturalistic study

CONCLUSIONS

- Bipolar disorder is a complex condition that can be effectively managed under the paradigm of personalized medicine
- Patients can be stratified according to biological, clinical, and staging features
- The polarity index, a measure of the relative prophylactic efficacy of drugs, may be a useful tool to guide maintenance treatment according to predominant polarity
- Early intervention and maintenance treatment is crucial for prevention of recurrences and their neurobiological consequences
- Further research is necessary to clarify the many remaining questions concerning maintenance treatment in BD in general, in particular regarding effective and safe treatment of depressive episodes in BD

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PARTICIPANTS

LIST OF PARTICIPANTS

Tânia Abreu
Filipe Almeida
Cátia Alves
Nuno Dinis Alves
Sara Luís Azevedo Pinto
Bernardo Barata
Francisca Bravo
Ana Catarina Campos
Bernardo Costa Neves
Nelson Couto
Filipe Couto Gomes
Chrysoula Dioli
Daniela Freitas
Daniela Lascasas
Catarina Lima
Sofia Lopes
Luís Martins Correia
Mónica Morais
Pedro Moreira
Joana Pereira
Anna Pliássova
Ana Poças
Carlos Portugal Nunes
Joana Reis
Joana Silva
Nuno Silva
Célia Soares
Carla Spínola
Maria Suárez Gómez
Ricardo Ribeiro
Nuno Trovão

ABSTRACTS

Tânia Abreu
A prospective study of patients with Bipolar Affective Disorder. Aims: Characterize the patients; episodes; and euthimic period. Assess adherence to therapies; quality of life and disease's impact. Study Design: *Sample*: inpatients admitted at the Department of Psychiatric and Mental Health of the Hospital Center Tâmega e Sousa with Bipolar Affective Disorder Type 1 and 2. *First evaluation when admitted*: complete anamnesis and structured evaluation with the following instruments: WHO QoL-BREF; Pittsburgh Sleep Quality Index; Young Mania Rating Scale; Hamilton Rating Scale for Depression and Anxiety; Suicidal Ideation Questionnaire; SAPS; TEMPS-A; Composite Scale of Morningness. *Follow-up after discharge*: 1 month, 6 months and every 12 months for 4 years.

Filipe Almeida
Clinical Vignette: R., 59 year old nun, diagnosed with Parkinson's Disease in 2006. By September 2014, after her brother's death from colorectal cancer, R. began recurrent negative thoughts on this subject. 2 months before commitment, delusions of guilt and auditory hallucinations developed. At admission, by February 2015, R. described accusatory voices and believed severe sins would cause her to be expelled from the congregation. Obsessive traits were apparent and fellow nuns reported severe hoarding behaviour. Previously medicated with: Ropinirole 8mg i.d.; L-DOPA 200mg+Carbidopa 50mg+ Entacapone 100mg t.i.d.; L-DOPA 200mg+Carbidopa 50mg (Controlled Release formulation) i.d.; Sertraline 100mg i.d.

Cátia Alves
Validation of an automated equipment for depression induction in a rodent model. I am currently developing my master thesis on the pre-clinical field in a start-up located in University of Minho. The aim of my research is to induce chronic stress in rats with automated equipment, developed to bring a more homogeneous approach to the depression induction in rats. The validation of this equipment could contribute to standardize the process, thou improvement is still required. In that way, I would like to discuss some alternatives to minimize variability and mimic better the human disease. Additionally, it would be also interesting to debate new ways of assessing the induced phenotype and explore both the potential and limitations of these animal models.

Nuno Dinis Alves
We intend to better understand the mechanisms behind the persistent effects of depression and comprehend the involvement of adult neuroplasticity including adult hippocampal neurogenesis in the therapeutic effects of antidepressants. Additionally, we are pursuing the definition of new biological markers to follow the course of the disease and predict recurrent episodes.

Sara Luís Azevedo Pinto
Estrogens and Psychosis: a possible therapeutic target? Gender differences in the clinical course of psychosis have been described. Estrogens may play a role in this difference. The estrogen hypothesis regarding schizophrenia highlights that estrogens have a neuroprotective role in susceptible women, reducing the risk or postponing the development of psychotic illness. Recent studies showed that cognitive performance of women with schizophrenia treated with raloxifene improves. Moreover, in the post-partum period and menopause there is a higher incidence of psychotic episodes. It is important that future studies clarify the role of estrogens, both in the pathophysiology and therapy of psychotic illness.

Bernardo Barata
Bipolar disorder (BD) is a severe mental condition influenced by multiple factors. Climate and weather conditions are thought to trigger and influence symptoms of BD, however methodological limitations in studies addressing this area of research have hampered the accurate analysis of a causal link between meteorological variables and mood episodes. Our team is reviewing the literature and plans to study the relationship between meteorological variables and mood episodes in a population of bipolar patients. At the time of the ECNP seminar, we may have results to present and, if appropriate, potential underpinning mechanisms and therapeutic implications may be discussed.

Francisca Bravo
Alzheimer's disease (AD) is the most common form of late-onset dementia. Its pathology is characterized by the accumulation of amyloid-beta and impaired phosphorylation of tau. Also, endocytosis and membrane trafficking are known to be affected in AD pathogenesis. Recently, human genetic studies have identified bridging integrator 1 (Bin1)/amphiphysin 2, an endocytosis modulating protein, as a major risk factor for AD. Moreover, the lipid modifying phospholipase D (PLD) isoenzymes, PLD1 and PLD2, were shown to modulate the cognitive deficits in an AD mouse model. In light of the previous reported finding the Bin1 interacts both with PLD enzymes and with tau, we hypothesized that a potential protein complex comprising PLD/Bin1/tau could have a role in the pathogenesis of AD. To address this hypothesis we will rely in a multidisciplinary approach using neuronal cell lines, primary neuronal cultures from PLD and tau knock-out mice and AD mouse models.

Ana Catarina Campos
Clinical vignette of a patient which presents a diagnostic/treatment dilemma: Woman of 61 years old, retired (teacher), born in Guinea. Came to the emergency department in the context of psychosis with a few years of development, characterized by a disorganized, incoherent, confabulatory and fantastic-themed speech; thought derailment; Fregoli delusion; and poorly organized persecutory delusions. With visual hallucinations. She elaborated several disorganized texts directed to the Town Council and UEFA president, as well as very incoherent tales for children. Without cognitive deterioration or depressed mood. Analytical test results were normal apart from slightly increased CRP. A head MRI revealed a vestibulocochlear schwannoma on

the right side. She was observed by a Neurology specialist that excluded organic neurological causes for the symptoms.

Bernardo Costa Neves
A rapidly emerging field of research suggests that the gut influences mood and behaviour. This study aims to test the hypothesis that a depressive phenotype can be transferred via the gut microbiota. For this study, maternal separation (MS) would be used as a rodent model of depression. Germ free rodents would then be colonized with gut microbiota isolated from MS rodents. Behavioural testing would finally be used to assess depression- and anxiety-like behaviour in the recipient animals. It is expected that the recipient animals develop altered behaviour following colonization.

Nelson Couto
Pharmacotherapy for treating female sexual dysfunction. There have been 26 medications approved by the FDA for the treatment of male sexual dysfunction but none for FSD. A recent (2014) hypothesis on-demand by combining testosterone with either a psychoactive agent (buspirone) or a PDE-5 Inhibitor (sildenafil) to enhance the neuroendocrine balance between sexual excitation and sexual inhibition have been promising results. After reviewing the available studies on pharmacotherapy for FSD, the author will try to apply other 5-HT1A receptor agonist like trazodone, and bupropion, in combination with testosterone to a cohort of patients with DSM-V diagnosis of Female Sexual Interest/Arousal Disorder.

Filipe Couto Gomes
Clinical vignette: Mr. P. is a 67 year old man with a history of several psychotic episodes, and several depressive episodes with suicidal attempts, starting at the age of 23, and he's otherwise healthy. With risperidone, 6 mg per day, he maintains mystique delusions. A dose increase failed due to adverse effects. His wife complains that Mr. P. is usually apart of the family's activities, although he takes their grandson to school everyday, helps with several domestics chores, and he's keen on participating in his church's tasks (which he often has problems to accomplish correctly).

Chrysoula Dioli Exploring the mechanistic role of Tau protein in stress-evoked damage of adult neurogenesis. Tau is a cytoskeletal protein involved in cell division and differentiation while its hyperphosphorylation has been causally related to neuronal atrophy and diminished neurogenesis in Alzheimer's disease. Chronic stress, a well known "sculptor" of adult brain plasticity, reduces hippocampal neurogenesis but the underlying mechanisms remain unclear. As we previously showed that chronic stress triggers Tau hyperphosphorylation and cytoskeletal disturbances, hereby, we monitored the potential involvement of Tau on stress-driven changes of neurogenesis. Our results suggest that absence of Tau blocks the stress-driven reduction of neurogenesis, but not astrogenesis, in adult hippocampus highlighting the role of Tau in stress-damaged brain plasticity.

Daniela Freitas
Olfactory reference syndrome is a rare psychiatric condition. Past classifications considered it as a delusional disorder, but a variety of studies showed that the disorder responded better to antidepressants than to antipsychotics, so that current classifications mention it as being related to obsessive-compulsive disorder. The aim of this vignette is to discuss some troublesome and complex issues of diagnosis and management of patients with olfactory reference syndrome, by reporting the case of a 38-year-old woman who presented with the condition. Data on olfactory reference syndrome are still limited and more research in this field is needed, in order to establish its nosological status.

Daniela Lascasas
Some atypical antipsychotics have been associated with increased rates of metabolic abnormalities. Patients treated with this antipsychotic medications have increased rates of metabolic syndrome when compared to the general population.
However, convenient metabolic abnormalities surveillance in this risk group is not allways performed. Therefore, it would be important to know the prevalence of metabolic syndrome in antipsychotic-treated patients of our region, under the action of Psychiatry and Mental Health Department of ULSNA (Unidade Local de Saúde do Norte Alentejano), in Portalegre district, in order to raise medical awareness on this condition and to develop preventive strategies.

Catarina Lima
Compulsivity, defined as the maladaptive repetition of behaviors that have ceased to serve its purpose, is a feature of psychiatric diseases such as obsessive-compulsive disorder and addiction. In order to better understand the neuronal circuits underlying this type of behavior and the impact of chronic stress on its expression, we propose to analyze the performance of rats on a recently developed behavioral paradigm that allows for the assessment of perseverative responding, the variable delay-to-signal. By targeting specific brain regions involved in decision-making processes, such as the orbitofrontal cortex, we intend to modulate our animals' behavior through optogenetic manipulation.

Sofia Lopes
Depression and Alzheimer´s disease (AD) exhibit commonalities in their clinical profile. Chronic stress is causally related to both disorders while our studies suggest that stress triggers AD mechanisms such as APP misprocessing by activating BACE1 enzyme. Based on this, we aimed to clarify the link between AD-related mechanisms and depression. We show that stress-triggered depression was accompanied by increased APP misprocessing and neuronal atrophy while antidepressant reversed these effects. In addition, we demonstrate the blockage of stress-triggered depressive behavior and synaptic atrophy in animals lacking APP misprocessing, further supporting its involvement in depressive pathology and behavior.

Luís Martins Correia
Introduction: Suicide is a common endpoint for patients with bipolar disorder. The identification of those at risk of committing suicide enables its prevention. Objective: The identification of functional brain differences between those patients with bipolar disorder presenting acute suicidal behavior and those patients with the same illness, but without present or past history of suicidal behavior. Methods: Patients with bipolar disorder who seek care at the emergency room presenting acute suicidal behavior are compared, in a fMRI analysis, to those with the same illness but without present or past history of suicidal behavior based.

Mónica Morais
Antipsychotic drugs in depression: the unexplored role of neuroplasticity Recently, some atypical antipsychotic drugs have received FDA approval for the treatment of antidepressant-resistant forms of major depression. Growing evidence suggests neuroplasticity impairments involved in the pathogenesis and recovery from depression. However, the impact of antipsychotics in the modulation of this phenomenon remains widely undisclosed. To address these questions, an unpredictable chronic mild stress paradigm (uCMS, 7 weeks) was implemented to induce depressive-like behavior in rats. Antipsychotic drugs from different pharmacological classes, clozapine and haloperidol, were daily administered (during the last 3 weeks of uCMS). At the end, behaviour and molecular analysis were performed. The results suggest an association between the modulation of neuroplasticity (adult neurogenesis) and the emotional and cognitive changes observed in response to different classes of antipsychotic drugs in an animal model of depression.

Pedro Moreira
Obsessive Compulsive Disorder (OCD) is one of the most handicapping psychiatric conditions. The neurobiological mechanisms of OCD are inconclusive with several heterogeneities being reported between studies. It has been hypothesized that this may be related with the inclusion of distinct subtypes of the disorder. It has been advocated that distinct subtypes are associated with different brain structural and functional alterations. In this project, we intend to contribute for the knowledge of OCD. For this purpose, we will conduct a comprehensive characterization of structural and functional brain patterns.

Joana Pereira
Schizophrenia is a complex psychiatric disorder that among other features is characterized by social withdrawal. Several brain areas have been linked to this pathology, namely the hippocampus, in which occurs the proliferation of stem cells in the adult brain. However, most of the studies only target the evaluation of new neurons and the relevance of astrocytes is still unknown. In this study, we propose to evaluate the effects of different antipsychotics in animal sociability and in the formation and morphology of astrocytes as well as the expression of astrocytic-related genes in the hippocampus and possibly find a link between these dimensions.

Anna Pliássova
Increased density of glutamatergic nerve terminals and decreased density of adenosine A1 receptors in the amygdale of suicide completers. Amygdala is one of the affected structures in depression. Adenosine receptors (AdoR) regulate synaptic efficiency in amygdala. We tested if suicide completers displayed a synaptic imbalance and changes of AdoR levels. We compared postmortem tissue samples from male suicide completers with age-matched controls. AdoR are present at synapses. A_1R density was lower in total extracts of suicide completers and there were no changes in A2AR density. Also, there was an increased density of glutamatergic nerve terminal markers in the amygdala of suicide completers. These results suggest a possible role of amygdala A_1R in depression.

Ana Poças
In schizophrenia, the patient in acute phases of his illness does not have insight about his medical condition or actions. It's estimated that 90% of patients with schizophrenia only adhere partially to the treatment. The use of depot medication is an option for these patients. We analyzed the relationships between patients in compulsory treatment taking only oral antipsychotics and those who were taking depot antipsychotic. There were no statistically significant differences between the two groups in the probability of adherence to medication, in personal and social function, or in the predominance of negative/positive symptoms.

Carlos Portugal Nunes
Prevalence of depression is 2-fold higher in those with diabetes compared to general population. Insulin and IGF-1 have neuroprotective/neurotrophic properties indicating that central insulin resistance (IR) may contribute to the progression of depression. The mechanisms underlying this association are not yet fully understood. Nevertheless, The neuroactive peptides, insulin, IGF-1 and incretins, or agents that facilitate their central effects (e.g. DPP-4 inhibitors), may constitute novel treatments for depressive disorders. Using animal models, we intend to characterize brain alteration associated with depression and IR and test the protective effects of incretin-based therapies in the development of depressive-like behaviour. Also, we will use an fMRI approach to study neural activation in depressed individuals with or without IR under respective treatments.

Joana Reis
My current research interest is the identification of EEG-fMRI correlates of emotional response in MDD patients. The short-term effects of antidepressant drugs in brain are poorly understood and their correlates in fMRI and EEG activations unexplored. The aim is to study brain alteration caused by anti-depressive drugs through the simultaneous acquisition of fMRI and EEG during resting state, executive function and emotional evocative tasks. This study aims to clarify the biological mechanisms by which anti-depressive drugs act in the brain alleviating the depressive symptoms. I expect to identify EEG- fMRI correlates of drug-targeted neurophysiological alterations responsible for the depressive symptoms amelioration.

Joana Silva
Antipsychotic Long-acting Injections and Sexual Dysfunction. Sexual dysfunction has been reported as a side effect of all antipsychotics. The rate of sexual dysfunction in patients taking risperidone and haloperidol long-acting injections is similar. There is scarce data about antipsychotic long-action injections and sexual dysfunction, despite well documented mechanisms of action. Our purpose is to study the relationship between sexual dysfunction and antipsychotic long-action injections, using a group of pre-selected patients, who answered the Arizona Sexual Experience Scale. Despite of being a pilot study, with only 30 patients, in this population is more likely to have sexual dysfunction when a patient is on risperidone, than on haloperidol.

Nuno Silva
Systemically administered riluzole and magnesium chloride have been widely investigated as neuroprotective agents in animal models of spinal cord injury (SCI) and were found to promote both locomotor improvements and tissue sparing after SCI. Therefore, we aimed to investigate the neuroprotective efficacy the combined administration of these drugs. SCI animals were randomly distributed to receive: 1) riluzole (2.5 mg/kg,) 2) magnesium chloride (24.18 mg/kg) 3) a combined treatment (riluzole and magnesium), or 4) saline. Subsequent treatments were given in 4 intraperitoneal injections (spaced 12 hours apart). Our results show that only the riluzole treatment significantly improved behavioral recovery, promoted tissue sparing, diminished lesion volume, increased seratonergic fiber sparing and axonal preservation in the caudal portion of the spinal cord. The combined treatment, although simultaneously targeting several excitotoxic-related mechanisms, did not further improve behavioral and histological outcome when compared with riluzole given alone.

Célia Soares
From the skin to the brain. Introduction: Psychiatric disorders have long been linked to both immune system activation and alterations in serotonin (5-HT) signalling. On the other hand pharmacological regulation of the serotonergic system may modulate immune function and provide therapeutic options for organic diseases with an inflammatory compound. Psoriasis is a very well studied immune disease in which psychiatric comorbidities are very frequent. Objective: To study how immune system function of psoriatic patients correlates with psychiatric comorbidities and analyse alternative treatment options. Methods: In a sample of psoriatic patients measure C-reactive protein (CRP), tumour necrosis factor (TNF)-a, interleukin (IL)-6, leptin, resistin and adiponectin levels; register the presence of psychiatric comorbidities or psychopharmacological treatment and analyse how the variables “immune system function”, “psychiatric comorbidities” and “clinical manifestations of psoriasis” correlate over the treatment of psoriasis.

Carla Spínola
A 69 year-old woman, with a known history of bipolar disorder, was admitted into our Acute Psychiatric Inpatient Unit with depressed mood, mutism, akinesia, repetitive falls, and rapid deterioration over the previous year. Examination revealed an overlong speech latency, axial rigidity with retrocollis, extreme bradykinesia, postural instability, shuffling, and broad-based gait. Brain MRI showed superior cerebellar peduncles atrophy (Mickey Mouse sign). We assumed a working diagnosis of progressive supranuclear palsy. A therapeutic trial with L-DOPA showed transient improvement of akinesia. An off-label trial with methylphenidate produced a striking improvement in bradikinesia and mood after just one dosis (20 mg).

Maria Suárez Gómez
Bipolar disorder is caused by the combination of genetic and environmental factors. Genetic analysis has identified genes whose dysfunction might predispose to the disorder. The response of patients to lithium and valproate show that genes encoding miRNA´s might be involved. These non coding RNA elements regulate gene expression and could participate in the development of diseases such as cancer, heart disease and mental and neurological disorders. Because the administration of mood stabilizers has been found to modify the expression of some miRNA´s, this suggests that the knowledge about these mechanisms could help diagnose some cases of bipolar disorder identifying plasmatic molecular markers.

Ricardo Ribeiro
Introduction: A small proportion of video game players develop uncontrolled gaming behavior. It occurs frequently in the early age, and can lead to structural and functional brain modifications, like others substance addictions, and in the future a personality dysfunction with economic and social costs. Objective: Study structural and functional brain modifications on video game addicts. Methods: Comparing a group of video game addicts with a group of substance use disorders, and healthy controls, matched age and the same lifetime substance/video game exposure. Comparing through magnetic resonance imaging, paradigms of fMRI, and personality scales.

Nuno Trovão
Neurobiological correlations between Anxiety, Depression and Obsessions-Compulsions. The so far partially known moderate overlapping of neural circuitry behind pathophysiology of anxiety, obsessions and depressive affects may account for the hypothesized clinical relationship among them. Obsessive symptoms may be secondary to depressive ones, “depressive-anxious” syndrome is widely described in clinical practice and unifying psychological theories focusing on core emotional processing have emerged. After reviewing the available neuroimaging studies, the author soughs to elucidate which components of affective circuitry overarch all these potentially linked symptoms and so explain the psychopathology neurobiology. A cohort of depressed, anxious and obsessive patients would be submitted to fMRI to depict relevant clinical-imagiological associations.