ECNP

ECNP-EPA
Seminar in Neuropsychopharmacology

27-29 April 2011
Viinistu, Estonia

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 aims to widen the knowledge of Neuropsychopharmacology. To fulfil this aim ECNP organises, amongst others, yearly the ECNP Congress that comprises at least 3 plenary lectures, 28 symposia and 6 educational update sessions. The latter sessions target issues such as updates on evidence-based treatment and new developments in the preclinical area that influence the clinical field. The ECNP Congress attracts more than 7,000 participants and is considered to be the largest event in neuropsychopharmacology in Europe.

ECNP also supports on an annual basis participation of 100 young psychiatrists and researchers in an intensive three-day Workshop in Nice. Furthermore ECNP has installed since 2009 the ECNP School on Neuropsychopharmacology in Oxford, United Kingdom.

Other activities of ECNP include the journal *European Neuropsychopharmacology*, *ECNP Matters*, the monthly e-news, webcasts of presentations of the Congress and the Workshops, and awards.

Finally, ECNP organises seminars, as the one you have been invited to participate, in areas where there are less opportunities for psychiatrists to participate in international meetings. So far, ECNP has organised this meeting in Czech Republic, Poland, Estonia, Turkey, Bulgaria, Romania, Slovak Republic and Hungary. Interaction is the keyword at these meetings and they have proven very successful both for the participants and for the faculty. We expect you to be very participative during this meeting and to to take the most advantage of it.

Please see the ECNP website (www.ecnp.eu) where you can find further information about the above initiatives and additional information.

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

Celso Arango, MD
Chair ECNP Educational Committee

European College of Neuropsychopharmacology

Who we are
and what we do

European College of Neuropsychopharmacology

ecnp

Goals

- Provide a uniquely broad interdisciplinary platform
- Apply new knowledge on fundamental disease mechanisms to clinical applications and vice versa
- Bridge the gap between basic research, clinical science and medical practice
- Pave the way for improved pharmacological treatments that will improve the quality of life of people suffering from mental disorders

Activities

- Annual congresses
- Targeted expert meetings
- Regional meetings
- Consultation meetings
- Awards

- Support for young scientists in Europe:
  - School of neuropsychopharmacology
  - Young scientist workshops
  - Seminar
  - Free or reduced registration at ECNP congresses

The benefits of membership

- Reduced registration fees at ECNP congresses
- Brainstorming sessions at ECNP congresses
- Free subscription to the ECNP journal, *European Neuropsychopharmacology*
- The *ECNP Matters* newsletter
- Access to the special members section on the ECNP website

Programme

ECNP-EPA Seminar in Neuropsychopharmacology
27 - 29 April 2011, Estonia, Viinistu

Wednesday 27 April 2011
Arrival of participants and experts
19.00 Welcome and dinner

Thursday 28 April 2011

09.00 – 09.15	Introductions to the programme
	Celso Arango, Spain
09.15 – 10.00	Neurobiology and treatment in early onset psychoses
	Celso Arango, Spain
10.00 – 10.45	Challenges of genetic research in psychiatry
	Marion Leboyer, France
10.45 – 11.30	Coffee break
11.30 – 12.15	Development of new targets for new drugs in psychiatry
	Sven Ove Ögren, Sweden
12.15 – 12.30	How to give a talk
	Celso Arango, Spain
12.30 – 13.30	Lunch

Presentations participants in 3 groups in 3 parallel workshops			
Round 1 13.30 – 15.00	*Celso Arango and Jaanus Harro*	*Sven Ove Ögren, Kaire Aadamsoo, Erika Saluveer*	*Marion Leboyer and Alexander Zharkovsky*
	Group 1	**Group 2**	**Group 3**

15:00 – 15.30	Coffee break
15.30 – 16.30	How to prepare a scientific paper
	Celso Arango, Spain and Jaanus Harro, Estonia
16.30 – 17.30	Discussion on career opportunities
18.30	Music performance and dinner

Friday 29 April 2011

Presentations participants in 3 groups in 3 parallel workshops			
Round 2 08.30 – 10.00	*Celso Arango and Jaanus Harro* **Group 2**	*Sven Ove Ögren, Kaire Aadamsoo, Erika Saluveer* **Group 3**	*Marion Leboyer and Alexander Zharkovsky* **Group 1**
10.00 – 10.30 Coffee break			
Round 3 10.30 – 12.00	*Celso Arango and Jaanus Harro* **Group 3**	*Sven Ove Ögren, Kaire Aadamsoo, Erika Saluveer* **Group 1**	*Marion Leboyer and Alexander Zharkovsky* **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   Time to fill out the evaluation forms and preparation
of awards ceremony
15.15 – 15.30   Short break
15.30 – 15.45   Awards ceremony
15.45 – 16.00   Concluding remark and thanks
Celso Arango, Spain

Celso Arango, MD, PhD

Professor Celso Arango MD is Head of the Adolescent Unit, Department of Psychiatry, Hospital Gregorio Marañón. He is also Associate Professor of Psychiatry at the Universidad Complutense de Madrid and Associate Professor of Psychiatry at the University of Maryland, School of Medicine in Baltimore and Consultant to the EMEA and AEM.

Professor Arango is a M.D. and Ph.D. and has a specialist degree in Forensic Psychiatry from the Universidad Complutense de Madrid. He is an instructor for two undergraduate courses and doctoral courses and thesis director for eight doctoral dissertations. He is the editor of fi ve books and more than 0 book chapters and has authored more than 50 scientifi c articles published international journals. In addition he has presented more than 00 papers and presentations at international conferences from 99 to 008. His research involvement includes participation in research projects, as principal investigator, Coordinator of a Thematic Network of the Instituto de Salud Carlos III (ISCIII) and Scientifi c Director of the the Spanish Network in Mental Health (Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM).

Professor Arango's memberships include the editorial committees of 0 Spanish and international scientifi c journals and the Executive Committee of the ECNP. He has 9 awards conferred by Spanish and international scientifi c societies and the Cross of Civil Merit in Health. In addition, he is the Coordinator of the "European Child and Adolescent Neuropsychopharmacology Network." He is also Secretary of the Spanish Society of Biological Psychiatry and member of seven other Spanish and international scientifi c/professional societies.

Professor Arango´s main areas of research included neurobiological correlates of earlyonset psychosis disorders, developmental neuropsychopharmacology and psychopharmacology in schizophrenia.

How to prepare a scientific presentation

Celso Arango

Before you start

- What does the audience already know about your topic?

- What are their interests?

- Why are you giving presentation?

Before you start

- What is your desired outcome?

- How much time do you have?

- What are key points?

Common Causes of Ineffective Presentations

- Failure to prepare the talk
- Confusing structure/not giving take home messages
- Gaps in logic
- Poorly designed slides
- Poor delivery

Organizing a Presentation

i. Outline
ii. Problem and background
iii. Design and methods
iv. Major findings
v. Conclusion and recommendations

Making slides

- Main points only
- One idea per slide
- Short words, few words (5 per line)
- Strong statements: active voice

The start

- Let audience know what they are going to hear
- Let them know how the presentation will be organized

Start broad, get specific, and end broad

The middle is your original contribution
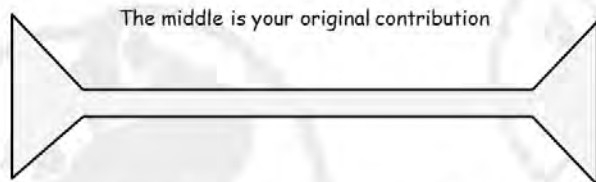
Start with the biggest questions and get progressively more specific

Focus now on conclusions

Audience attention curve
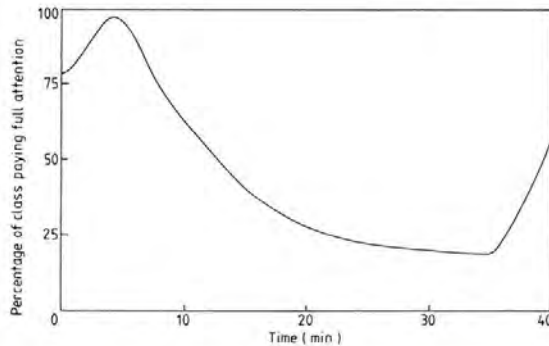
Conclusion and Recommendations

- Key points

- Implications

- One slide for each message

Slide 1:

European College of Neuropsychopharmacology
ecnp

Formal aspects

- AVOID USING ALL CAPITAL LETTERS BECAUSE IT'S REALLY HARD TO READ!
- Dark letters against a light background (or the opposite) work
- Avoid some colour combinations (red-green)

Slide 2:

European College of Neuropsychopharmacology
ecnp

Formal aspects

- Choose style that supports the tone
- Apply the same style to each slide
- **Don't Say It, Show It**

    Be consistent!

And do not forget to…….

Relax

Listen to what you are saying

Pace and time yourself

And do not forget to…….

Face the audience

Never underestimate your audience!

With time you will enjoy…..

How to prepare a manuscript

Celso Arango

Categories

- Original research (focus of this talk)
- Reviews (invited vs. not invited)
- Case reports/series
- Letter to the editor

The Journal

- – Does the article fit the aims and scope of the Journal?
  - Choose before writing
  - General vs. subespecialty journal
- Read the table of contents of potential journals
- Examine several articles in potential journals
- Which journals will you cite in your article?

Sequence

- The syndrome of the blank screen
- Figures, tracings, tables
- Methods and Results
- Discussion and Introduction
- Abstract and Title

Tables and Figures

- Do before writing

- Exceed 1 sheet: redraw

- If small: move data to text

- Should be able to stand alone

Methods

- Draft can be made while doing the study

- Enough information for an experienced investigator to repeat your work

- Avoid tiresome detail

- Tables preferred to long list of numbers or statistics

Methods

- Refer to data (Fig. X, Table Y)
- Do not repeat numbers in Tables
- Include ethics information (with Ethics Committee approval and i.c.)
- Include complete statistics section

Discussion

- First paragraph
  - State major findings
- Last paragraph
  - "In summary…" (2-3 sentences)
  - "In conclusion…" (biggest mensage, return to Intro, avoid speculation, avoid "need more work"

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Discussion

- Middle paragraphs
    - Base each on a major result
- Always focus on your results
- Explain what is new without exaggerating
- Never discuss prior work without reference to your work (but do not forget appropriate identification of prior research)

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Discussion

- Refer Tables and Figures
- Do not repeat results
- Include limitations section

Introduction

- Keep it short. In most cases 3 graphs make it.
  - 1. Why the study is interesting (broad)
  - 2. Why did we do it? (specific)
  - 3. Hypothesis

Abstract

- Is your visiting card
- In most cases make the editor to send the ms to reviewers or reject it.
- Some numbers, but not in excess
- Determines if paper will be read
- Is distributed freely in databases
- Avoid acronyms

Title

- Max information in least words
- The title is an invitation to read the paper
- Use catchy titles
- State results

Keywords

- Make them easy for indexing and searching! (if you want to be cited)

References

- Cite the Journal you are submitting the paper to
- Reviewers may be selected from your references
- Use editing programs
- Relevant and recent

The context

- Need stretch of several hours

- Avoid distractions: phone, e-mail

- Ideas come while writing

First draft

- Write as quickly as possible
- As if thinking out loud
- Get everything down
- Ignore spelling, grammar, style
- Correct and rewrite only when the whole text is on paper
- Do not split the manuscript among the co-authors

Introduction

- Context
- Study question
- Relevant knowledge on issue

Formal aspects

- Check narrative flow: tell a story that the reader wants to read from start to end
- Smooth transitions
- Writing improves in proportion to deletion of unnecessary words
- Keep senteces short

Formal aspects

- After the second draft send ms to your coauthors
- After the suggestions have been incorporated leave it for some time a re-read

Formal aspects

- **If you do not have time to check the spelling you may have not had time to check the quality of your experiments......**

Formal aspects

- Prepare article, figures and table according to the journal's 'Guide for Authors'
- Adherence to the style of the journal is crucial
- Check references
- Check and double check your work

Authorship

- Decided as early as possible

- The journal has instructions on who should/should not be an author

- Basically all authors should have done a major contribution to the study

Authorship

- Approval of final version must be obtained from all coauthors before submission

- The first author is primarily responsible for collecting and analyzing data, and writing

Authorship

- The manuscript is not under consideration elsewhere and will not be submitted elsewhere until a final decision has been made by the journal

- All funding sources must be acknowledged

- All conflicts of interest should be reported

Peer Review

- Authors write

- Reviewers comment

- Editors decide

- Readers read (only what they like)

Peer Review

- Peer review helps to determine the significance, contribution to what is already known and originality of research

- Most journals reject some paper prior to peer review (on basis of Editor's own evaluation)

- Usually 2-3 reviews sought (per manuscript)

Possible Decisions

- Reject (up to 90-95% in good journals, do not give up!)

- Major revisions required (it will be reviewed again, may be rejected)

- Minor revisions needed (usually accepted)

- Accepted (congratulations! Enjoy and celebrate!)

Response to the editor

- Reviewer´s are (almost) always right. Editor is always right.

- Response to all the comments in a nice and polite way

- Thank the reviewers for their contribution

When the study is negative

- If your result is not as expected, you should understand the reason. It may be something really new. (Must find out why it did "not work" in the expected way!)

Early Onset Psychoses

Arango, C.
Hospital General Universitario Gregorio Marañón, CIBERSAM, Madrid, Spain.

Early-onset psychosis (EOP) is a, severe, and heterogeneous condition in which the first manifestations of psychotic symptoms appear before the age of 18. EOP has been associated with a higher severity of developmental disturbances, higher rates of a family history of schizophrenia spectrum disorders, a greater frequency of cytogenetic perturbations, poorer functional and clinical outcome, and has been considered a marker of poor prognosis. The symptoms used to define EOP are shared by several diagnoses, mainly schizophrenia spectrum disorders and bipolar disorders. We have conducted longitudinal studies with this population showing, among other findings, that there is a progressive loss of gray matter during the first two years after the first psychotic episode that is larger than expected. Cognitive impairment and neurological signs lack of progression during this first years after the appearance of the psychotic symptoms will be also reviewed. Different clinical and sociodemographic factors have been related to the increase use of second generation antipsychotics (SGA) in children and adolescents. Additionally, the tendency to establish an earlier diagnosis of the psychiatric conditions and, thus, to start on medication at former stages, has mean that antipsychotic medications are now used in younger ages and during longer periods of time. Based on our own studies therapeutic strategies will be provided to treat this population.

Early onset psychoses

Celso Arango

Hospital "Gregorio Marañón", Madrid, Spain
Tallin April 2011

Epidemiology

❖ **Psychotic disorders account for about 5% of mental disorders in adolescence and around 20% in adolescent hospital units**

❖ **In around 25% of cases, schizophrenia starts before 18 years of age**

❖ **Importance of early treatment for prognosis**

Loranger AGP, 1989; Beratis et al Schiz Bull 1994;
Briden et al 2001; Arango et al Eur Neuropsych 2005

Frequent symptoms in early onset psychoses

- Language disorders
- Difficulty distinguishing real and oniric world
- Auditory and visual hallucinations
- vivid and bizarre ideation and thoughts
- Lack of interest, desorganized thinking
- Labile mood
- Bizarre behaviour, stereotypies, lack of inhibition
- Delusions of reference
- Regressive behaviour
- Anxiety and severe fear
- Difficulties in social relationships

What you should ALWAYS ask for in a first psychotic episode

Hemogram

Biochemistry

Drug urine screen

Thiroid hormones

Pregnancy test in females

EEG

CT/MRI

Other depending on the form of presentantion, atypical symptoms, phenotypic markers, etc

Epidemiology: SZ in children and adolescents

- Prevalence: < 1/1,000
- Higher male-to-female ratio → as age increases, ratio even out
  - Onset usually 5 years earlier in males versus females
- Age at onset
  - Very rare before the age of 9 years
- Most patients present with pre-morbid abnormalities
- Type of onset
  - Usually insidious, specially in males
  - Acute onset in 25% of the cases

EARLY ONSET SCHIZOPHRENIA

Negative symptoms more frequent and persistent (prodromic phase)

In first episode schizophrenia affective symptoms are more frequent (specially labile mood)

Passivity phenomena, formal thought disorders and incoherence are less frequent than in adults.

Delusions less frequent and less complex

EARLY ONSET SCHIZOPHRENIA

Content of delusions related to age

Hallucinations are less integrated in the psychotic system

Very frequently motor disturbances are present (rigidity and clumsiness)

Phobic and obsessive behavior (feelings of bizarreness, artificiality, obsessive automatism)

Hallucinations:

- Present in normal children, anxiety disorders, adaptative disorders, sensory deprivation, PTSD, affective disorders.

- Prevalence in EOS: 80%. Prevalence in child depression: 18-40% (Freeman et al 1985)

- Not stable, affective resonance, lack of insight, congruent not congruent (RO dissociative disorders), no amnesia (RO epilepsy) (Caplan 2002)
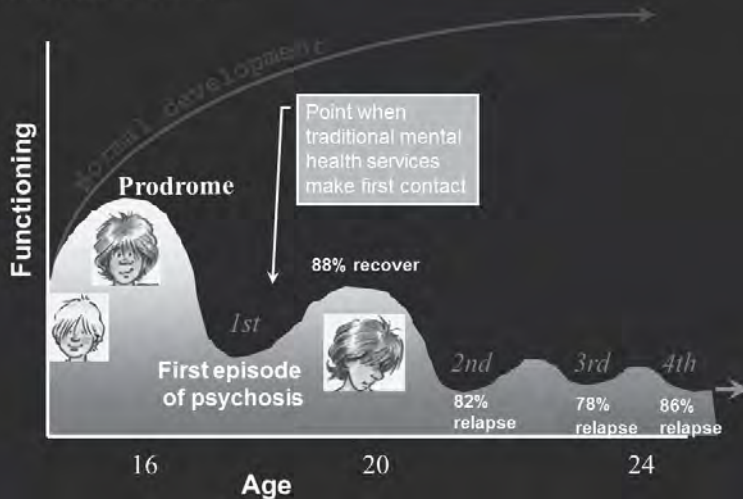
Differential diagnoses

- **Major depression with psychotic symptoms**
- **Schizoaffective disorder**
- **Bipolar disorder**
- **Dissociative disorder and PTSD**
- **Factitious disorder**
- **OCD**
- **PD**
- **Drug induced psychoses**
- **Epilepsy**
- **Personality disorder:**
  - **schizoid, schizotipy, paranoid and borderline**

Traditional Course of First Episode Psychosis

Adapted from Robinson et al, 1999

Functioning

Normal development

Prodrome

Point when traditional mental health services make first contact

88% recover

1st

First episode of psychosis

2nd — 82% relapse

3rd — 78% relapse

4th — 86% relapse

16   20   24

Age

Diagnosis of Schizophrenia in children

- ## Misdiagnosis

  American Academy of Child and Adolescent Psychiatry (AACAP) guidelines suggest 3 main reasons:

  – Rarity of diagnosis in paediatric population

  – Co-morbidity of symptoms (eg. substance misuse) & developmental disabilities

  – Hallucinations often as a result of illnesses other than schizophrenia (eg. OCD)

American Academy of Child and Adolescent Psychiatry. *J Am Acad Child Adolesc Psychiatry.* 2001;40:4S-23S

Diagnosis of Schizophrenia in children

- ## Reluctance to Diagnose

Accurate diagnosis often more difficult than in adults:

– Overlap of symptoms with other disorders

– Social stigmatization

– Changing symptoms during development

American Academy of Child and Adolescent Psychiatry. *J Am Acad Child Adolesc Psychiatry.* 2001;40:4S-23S

EPIDEMIOLOGY

❖ Kraepelin documented onset before age 10 in 4 out of 903 manic-depressive patients (Kraepelin 1921).

❖ Hypomania in 13% of adolescents (Carlsson, Kashani, 1988).

❖ Hospital discharge with BP diagnosis in 1996 was 1.3 per 10,000 U.S. children and 7.3 per 10,000 U.S. children in 2004. Adults showed a more modest, though still marked, rise of 56% (Blader and Carlson 2007)

Age of onset distribution for BD

Age at first episode (mean = 19.8, median = 17.5)
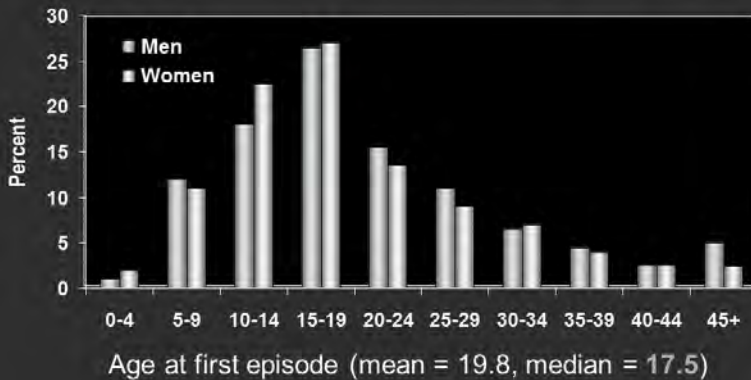
Diagnosis: conservative vs liberal

Narrow phenotype: euphoria, grandiosity, and classic manic symptoms

Broad phenotype: irritability and non-specific mood lability

Diagnosis: conservative vs liberal

Against broad phenotype:
  Drug side-effects
  Stigma
  Heterogeneity in etiological studies

In favour broad phenotype:

  Importance of early intervention in a critical period (Bipolar disorders in children associated with delay in treatment, greater severity, higher suicidality, and poorer prognosis (Lish et al 1994, Jerrell & Shugart 2004, Perlis et al 2004))
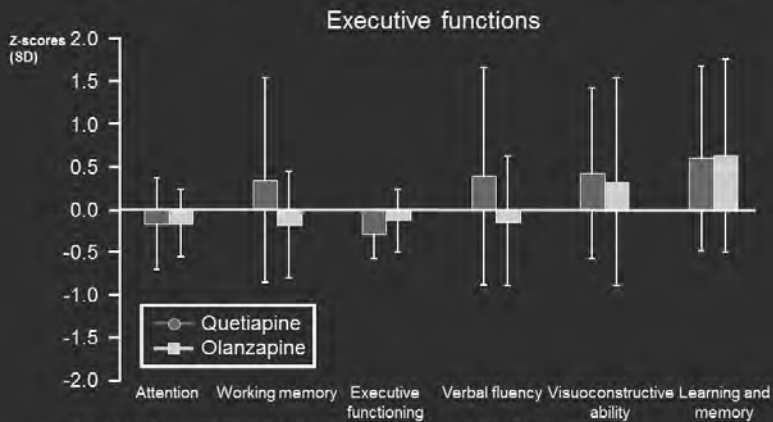
Prescribing Trends

Increased prescribing (USA):

x6 1993: 201,000 young people on antipsychotics
2002: 1,224,000 young people on antipsychotics
(Olfson et al., 2006)

2000-2002: 92.3% of prescriptions for antipsychotics were for second-generation antipsychotics (SGA) *(Olfson et al., 2006)*

Cognition: Tasks grouped in cognitive domains

Executive functions

- No cognitive improvement was observed in any of the groups
- No differences between groups

Robles et al 2011

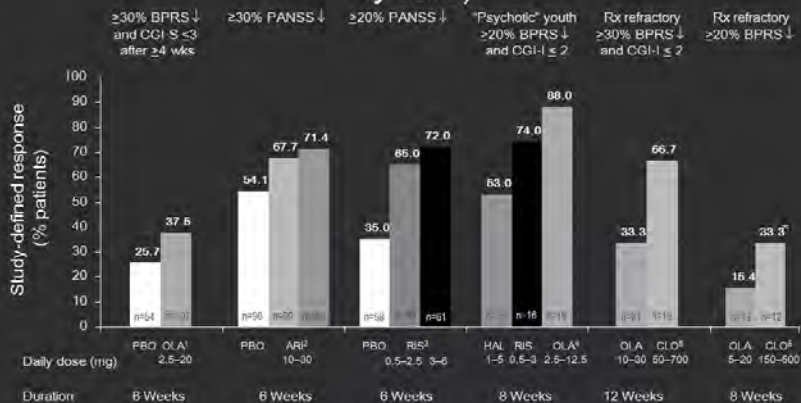Response in paediatric schizophrenia (8–17 years)

Figure adapted from listed references – studies do not reflect a direct comparison of data

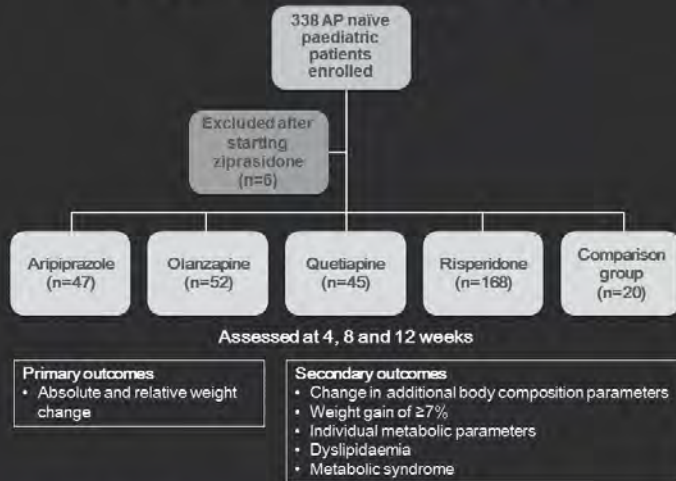1. Kryzhanovskaya et al. Poster presented at 44th Annual Meeting of ACNP 2005; 2. Findling RL et al. Am J Psychiatry 2008;165:1432–41; 3. Haas et al. Poster presented at: 160th Annual Meeting of APA, 2007; 4. Sikich et al. Neuropsychopharmacol 2004;29:133–45; 5. Kumra et al. Biol Psychiatry 2008;63:524–9, 6. Shaw et al. Arch Gen Psychiatry 2006;63:721–30.

Response Rates (≥50% Reduction in YMRS Total Score) in Pediatric Bipolar D/o: NNTs=3-6
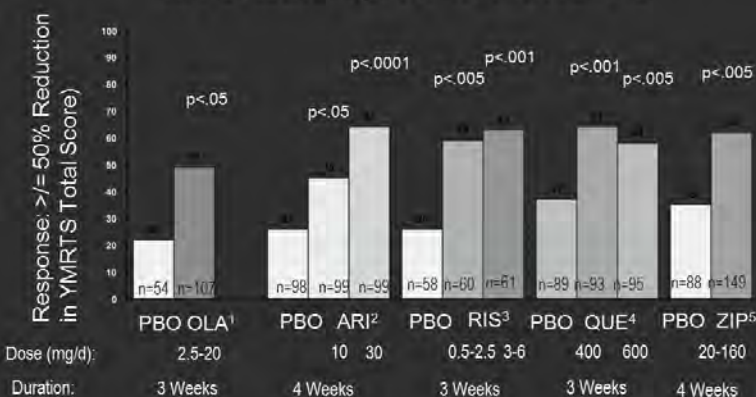
1. Tohen M, et al. Am J Psychiatry. 2007;164:1547-56; 2007;
2. Chang KD, et al. AACAP Annual Meeting, October 25, 2007.
3. Pandina et al. AACAP Annual Meeting, October 27, 2007.
4. DelBello MP, et al. AACAP Annual Meeting, October 25, 2007.
5. DelBello MP, et al. APA Annual Meeting, May 2008.

SATIETY study design

338 AP naïve paediatric patients enrolled

Excluded after starting ziprasidone (n=6)

| Aripiprazole (n=47) | Olanzapine (n=52) | Quetiapine (n=45) | Risperidone (n=168) | Comparison group (n=20) |

Assessed at 4, 8 and 12 weeks

Primary outcomes
- Absolute and relative weight change

Secondary outcomes
- Change in additional body composition parameters
- Weight gain of ≥7%
- Individual metabolic parameters
- Dyslipidaemia
- Metabolic syndrome

Correll CU, *et al. JAMA* 2009;302;1765–1773.

Treatment with all antipsychotics was associated with changes in metabolic parameters at 12 weeks

All values refer to mean change from baseline (p value)

	Aripiprazole (n=41)	Olanzapine (n=45)	Quetiapine (n=36)	Risperidone (n=135)	Untreated (n=15)
Weight (kg)	4.44 <0.001	8.54 <0.001	6.06 <0.001	5.34 <0.001	0.19 0.77
Fat mass (kg)	2.43 <0.001	4.12 <0.001	2.82 <0.001	2.45 <0.001	0.35 0.39
Waist (cm)	5.40 0.001	8.55 <0.001	5.27 <0.001	5.10 <0.001	0.70 0.40
Glucose (mg/dl)	0.54 0.76	3.14 0.02	2.64 0.12	1.14 0.26	0.69 0.81

Correll CU, *et al. JAMA* 2009;302;1765–1773.

Clinical Recommendations

• Evidence supports little difference in efficacy between treatments (with the exception of clozapine for treatment of resistant patients), but major differences in side effects.

• Children and adolescents have a higher risk than adults of experiencing adverse effects from antipsychotic medication

Clinical Recommendations

• Monitor metabolic adverse effects when using SGAs, particularly weight gain

• To avoid potentially serious health problems, clinicians along with patients and their families should jointly conduct a careful risk-benefit assessment when choosing an antipsychotic treatment.

Adverse Effect Monitoring of Children and Adolescents Treated with Antipsychotics

Assessment	Baseline	Routine Follow-up
Personal and family medical history	✓	Annually
Lifestyle behaviors	✓	Each visit
Sedation/drowsiness	✓	Each visit
Height, weight, BMI percentile, BMI z-score	✓	Each visit
Sexual/reproductive dysfunction	✓	During titration, then every 3 months
Blood pressure and pulse	✓	At 3 months, then every 6 months
Fasting blood glucose and lipids	✓	At 3 months, then every 6 months
Liver function tests	✓	At 3 months, then every 6 months
Parkinsonism, akathisia	✓	During titration, at 3 months, and annually (SAS or ESRS)
Tardive dyskinesia	✓	At 3 months and annually (AIMS)
Electrolytes, CBC, renal function	✓	Annually (more frequent blood counts if taking clozapine)
Prolactin	Only if symptomatic	Only if symptomatic
Electrocardiogram	If taking ziprasidone or clozapine	If taking ziprasidone: during titration and at maximum dose

(Correll, 2008)

50

Marion Leboyer, MD, PhD

Professor of Psychiatry,
University of PARIS-Est, France

Marion Leboyer joined the faculty of the University of Paris in 1998 as Professor of Psychiatry. Since 2002, she is head of the University affiliated Department of Psychiatry (Hospital Chenevier-Mondor, CHU Créteil, AP-HP) and runs a Psychiatry Genetic laboratory (INSERM). Dr. Leboyer's research efforts have contributed to a better identification of relevant phenotype for genetic studies, particularly in the field of bipolar disorder, schizophrenia, suicide and autism. Being principal investigator of national and international studies, she has been able to produce prominent findings such as identification in autism of the first mutations of genes implicated in synaptogenesis. She is director of .the FondaMental foundation, recently created by the French Ministry of Research, aiming at creating a network of expert centers and promoting research in Psychiatry. Dr. Leboyer has authored or co-authored more than 200 scientific articles and book chapters, as well as 5 books.

Marion LEBOYER
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E-mail : marion.leboyer@inserm.fr

CURRENT POSITION
Professor of Psychiatry, University Paris-Est
Head of the University affiliated Psychiatry Department, Groupe Hospitalier Chenevier-Mondor, in charge of a department of 123 psychiatric inpatients, a day hospital (30 beds), emergency unit, 3 outpatient consultation centers and 3 expert centers.
Head of the "Psychiatry Genetic" INSERM lab within Institut de Recherches Biomédicales de Mondor
Director of the Foundation FondaMental (Foundation for Research in Mental Health) created by the Ministry of Research

PUBLICATIONS
More than 200 original papers and review articles since 1984 (index M = 1.54), editor of 3 books

Main publications relevant to the lecture to be given at the ECNP – EPA Seminar

LEBOYER M, BELLIVIER F, NOSTEN-BERTRAND M, JOUVENT R, PAULS D, MALLET J.
Psychiatry genetics : search for phenotypes, *Trends in Neurosciences*, 1998, 21, 3 : 102-105
.

BELLIVIER F., GOLMARD J.L., HENRY C, LEBOYER M., Admixture analysis of age at onset in bipolar affective disorder, *Archives General Psychiatry* 2001,58,510-12.

BELLIVIER F, GOLMARD JL, RIETSCHEL M, SCHULZE T, MALAFOSSE A, PRIESIG M, Mc KEON P, MYNETT-JOHNSON L, HENRY C, LEBOYER M, Age at onset in bipolar in affective disorder: Further evidence for three subgroups. *American Journal of Psychiatry* 2003,160,5:999-1001.

JAMAIN S, QUACH H, BETANCUR C, RÅSTAM M, GILLBERG C, LEBOYER M, GILLBERG C, BOURGERON T, & the PARIS study. A de novo frameshift mutation of HNL4, an X-linked neuroligin, is associated with autism, *Nature Genetics* , 31 March 2003, 34, 27-29.

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ETAIN B, ET AL Genome-wide scan for genes involved in bipolar affective disorder in 70 European families ascertained through a BPAD type I early onset proband : Supportive evidence for linkage at 3p14 with a maternal parent of origin effect., *Molecular Psychiatry*, 2006 Mar 14 : 1-10

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Molecular Psychiatry, 2008, Jan, 13 (1), 90-8

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WEISS LA, ARKING DE; GENE DISCOVERY PROJECT OF JOHNS HOPKINS & THE AUTISM CONSORTIUM, DALY MJ, CHAKRAVARTI A
A genome-wide linkage and association scan reveals novel loci for autism.
Nature. 2009 Oct 8;461(7265):802-8

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TORO R, KONYUKH M, DELORME R, LEBLOND C, CHASTE P, FAU-CHEREAU F, COLEMAN M, LEBOYER M, GILLBERG C, BOURGER-ON T., Key role for gene dosage and synaptic homeostasis in autism spec-trum disorders, **Trends Genet.** 2010 Jul 5

AUTISM GENOME PROJECT, PINTO ET AL,
Functional impact of global rare copy number variation in autism spectrum, **Nature. 2010** Jun 9

LEBOYER M, KUPFER DJ.
Bipolar disorder: new perspectives in health care and prevention.
J Clin Psychiatry. 2010 Dec;71(12):1689-95

Genetic and environmental vulnerability factors in bipolar disorders

Marion Leboyer

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- University Paris –Est, Créteil, France;
- AP-HP, Henri Mondor-Albert Chenevier Hospitals, Department of Psychiatry, Creteil, France
- Foundation FondaMental

Objective
Despite the demonstrated high heritability of bipolar disorder, few susceptibility genes have been identified and linkage and/or association studies have produced conflicting results. This lack of replication has been accounted for by the use of invalid phenotypes, sample heterogeneity, unknown genetic parameters, and the underexploration of environmental aspects of the disease, which remain poorly understood.

Methods
This presentation will give examples of complementary approaches proposed to facilitate the identification of susceptibility genes in bipolar disorder.

Results
The first approach involves the identification of "candidate symptoms," rendering diagnostic entities presumably more likely to have a similar and simpler genetic basis. The candidate symptom approach has led to the identification of early-onset bipolar disorder (Leboyer et al, 2005) resulting in the identification of two genes involved in the phosphoinositidyl signalling pathway and of the association with a SNA25 promoter variant, through a genome-wide-association study (GWAs) (Etain et al, 2009 ; Jamain et al, subm).

The second approach relies on the genetic exploration of the severely disrupted circadian rhythms observed among bipolar patients. Exploration of candidate biological system, such as melatonergic pathway revealed mutations correlated with a decreased activity of the protein encoded by the gene acetylserotonin methyltransferase (ASMT) which is the last en-

zyme of the melatonin synthesis. Haplotype analysis of the gene showed a significant association with bipolar disorder (Etain et al, 2009).

The third approach involves the use of quantitative intermediate phenotype such as the measure of abnormal emotional reactivity in a GWAs analysis. Preliminary results showed that liability and intensity of emotions measured by two self rating scales might be influenced by genetic factors located on 13q31 and 18q21 (Etain et al, submitted).

However, narrowing down the phenotype into more homogeneous subtypes is insufficient to unravel the genetic background of bipolar disorder, and incorporation of environmental factors is probably needed to account for the multifactorial origin of bipolar. In particular, growing evidence suggests that early childhood trauma are frequent in bipolar disorder, impacts the clinical expression of the disease in terms of suicidal behaviour and age at onset, and may interact with genetic susceptibility factors underlying hyper-emotional reactivity.

Conclusion
Further exploration of this environmental factor and of its interaction with susceptibility genes will be proposed (Etain et al, 2008).

Leboyer M, Henry C, Paillere-Martinot ML, Bellivier F. Age at onset in bipolar affective disorders: a review. *Bipolar Disorder*, 2005; 7(2): 111-118.

Etain B, Dumaine A, Mathieu F, Chevalier F, Henry C, Kahn JP, Deshommes J Bellivier F, Leboyer M, Jamain S. A *SNAP-25* promoter variant is associated with early-onset bipolar disorder and a high expression in the brain, *Molecular Psychiatry,* January 2009

Etain B, Henry C, Bellivier F, Mathieu F, Leboyer M Beyond genetics: childhood affective trauma in bipolar disorder. *Bipolar Disord*. 2008 Dec;10(8):867-7

Genetic and Environmental factors in Bipolar Disorders

Marion Leboyer

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Psychiaty Genetic lab, INSERM U955, IMRB,
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Foundation Fondamental

Inserm
Institut national
de la santé et de la recherche médicale

UNIVERSITÉ
PARIS XII
VAL de
MARNE CONNAISSANCE ACTION

fonda Mental
Fondation
de recherche et de soins
en santé mentale

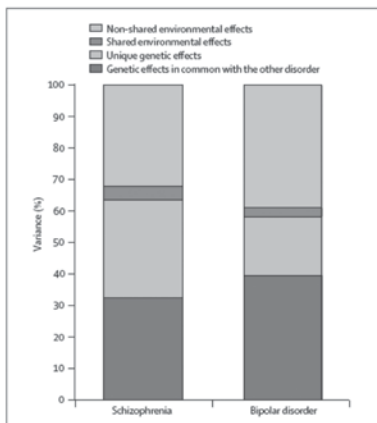
Genetic and Environmental factors in Bipolar Disorders

Figure: Variance accounted for by genetic, shared environmental, and non-shared environmental effects for schizophrenia and bipolar disorder

A very large study :

9 millions of Swedish subjects
40 487 bipolar patients

→ heritability of 60%

But also
→ environmental effects
→ Shared and non-shared effects
→ overlapping phenotypes

Lichtenstein P. Lancet 2009

What are the Strategies to identify Genetic and Environmental risk factors in Bipolar Disorder ?

1. PHENOTYPIC REFINEMENT

Candidate Phenotype : *Early Onset Bipolar disorder*
Intermediate phenotypes: *Emotional hyper-reactivity, Cognition*

2. GENETIC STRATEGIES

Non parametric method : **association study**, **GWAs**
Searching for biological pathway : **melatonin**, *phosphatidyl inositol..*

3. ENVIRONMENTAL FACTORS

Childhood trauma, *In utero infection, Cannabis…*

4. GENE x ENVIRONMENT INTERACTIONS

---

1. PHENOTYPIC REFINEMENT

Among patients
"Candidate symptoms"
Phenotypic components that have good **genetic validity**

- Intra-familial resemblance
- Homogeneous sub-forms
- High familial risk
- Genetic mode of transmission
- Assoc. candidate genes

ex: Age at onset
          Suicide

Among unaffected relatives
 "Endophenotypes"
Biological/cognitive/anatomical/electrophysiological measure of an *underlying genetic vulnerability*

- more frequent among relatives
- state-independent
- genetic mode of transmission
- assoc. candidate genes

ex: Memory deficits
          Circadian rhythm instability
          Emotional hyper-reactivity
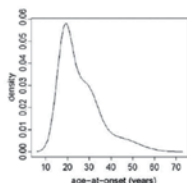
Leboyer et al, TINS, 1998
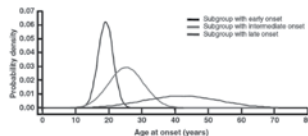
1. PHENOTYPIC REFINEMENT :
3 distinct age at onset subgroups
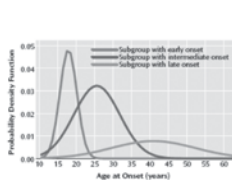
Bellivier 2001 & 2003   Hamshere 2008   Manchia 2008, Severino 2009

Early onset Bipolar subgroup is more homogeneous and more familial

- More manic episode than depressive, More psychotic symptoms

- Comorbid disorders : panic disorder, suicidal behavior, addiction, ADHD

- Rapid cyclers

- Poor lithium response

PHENOTYPIC REFINEMENT
Early onset bipolar disorder

21 yrs

Age at onset

Bellivier, Arch Gen Psychiatry, 2001

1. **A specific clinical profile**:
severe prognosis and instability
more comorbidity (ADHD, Alcohol abuse, suicide..)

2. Identification of age at onset threshold:
below 21 years

3. Age at onset of BPAD has a **strong familial component** :
   - Intra-familial resemblance (r=0.4, p=0.0001)
   - Elevated familial risk (**30%** versus 2%)
   - Segregation analysis : non mendelian major gene
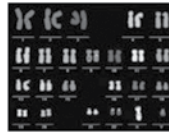
4. Association with **biological correlates**
   - Genetic markers
   - Cognitive profile
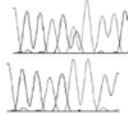   - Brain imaging

Reviewed in Leboyer et al, Bipolar Disorders, 2005

2. GENETIC STRATEGIES
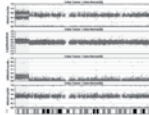to identify genetic risk factors
of early onset BPD

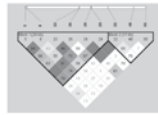Illumina 1 million SNP array
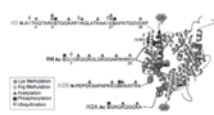French sample sizes : 800 BPAD

✦ Private mutations   ✦ CNVs   ✦ SNPs   ✦ Epigenetics hallmarks

⬇ + ⬇ + ⬇ + ⬇

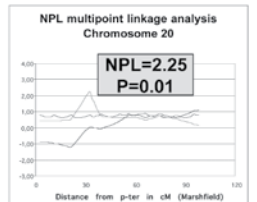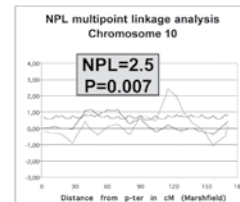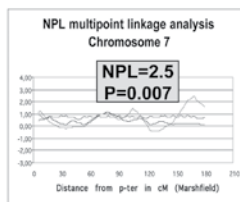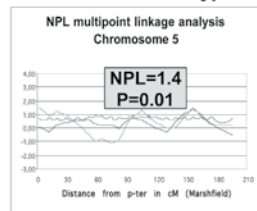# Bipolar Disorder

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Candidate Symptom : EARLY ONSET BIPOLAR DISORDER
Whole genome linkage analysis
multi-point regions detected with a p-value ≤ 0.01
Only in 84 european sib-pairs with an homogeneous and more familial subtype !

NPL multipoint linkage analysis
Chromosome 2

NPL=2.8
P=0.003

Distance from p-ter in cM (Marshfield)

NPL multipoint linkage analysis
Chromosome 3

NPL=3.5
P=0.0002

Distance from p-ter in cM (Marshfield)

NPL multipoint linkage analysis
Chromosome 5

NPL=1.4
P=0.01

Distance from p-ter in cM (Marshfield)

NPL multipoint linkage analysis
Chromosome 7

NPL=2.5
P=0.007

Distance from p-ter in cM (Marshfield)

NPL multipoint linkage analysis
Chromosome 10

NPL=2.5
P=0.007

Distance from p-ter in cM (Marshfield)

NPL multipoint linkage analysis
Chromosome 20

NPL=2.25
P=0.01

Distance from p-ter in cM (Marshfield)

Etain et al, Molecular Psychiatry, 2006

SNAP-25: A Candidate Gene in Region 20p12

Synaptic Vesicle Docking Fusion Protein, Synaptosomal-Associated Protein of 25 kDa
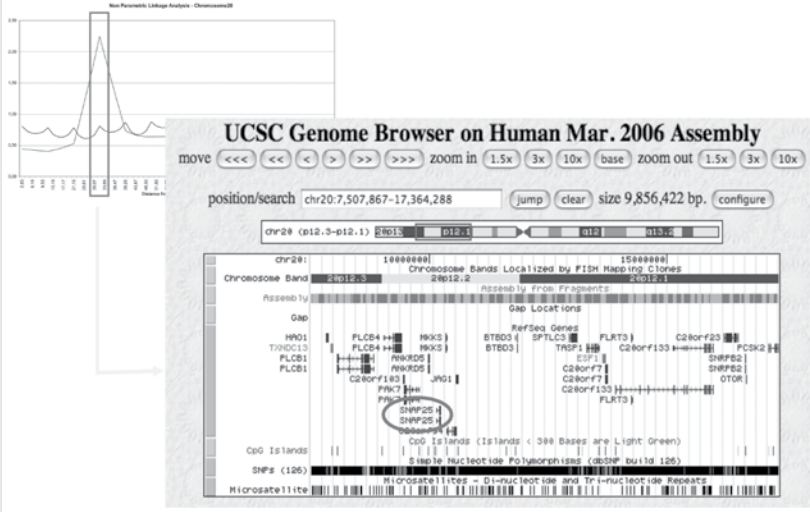
SNAP-25 : a candidate gene in region 20p12

synaptic vesicle docking fusion protein, synaptosomal-associated protein of 25 kDa

SNAP25 : a synaptic vesicle, involved in exocytosis, enabling vesicle fusion and catecholamines liberation

Variations of SNAP25 levels in brains of BP patients

A genetic risk factor of ADHD

Rizo and Südhof, *Nat Rev Neurosci* 2002

SNAP25 and early onset bipolar disorder

SNP4

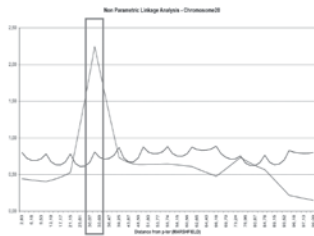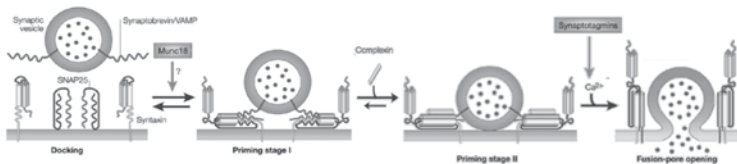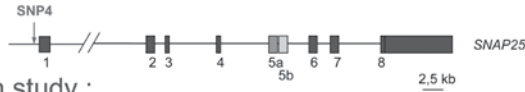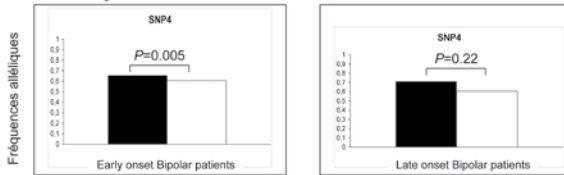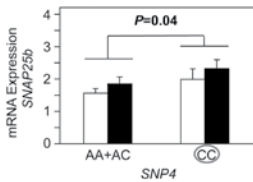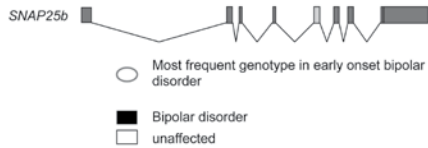1   2 3   4   5a 5b   6 7   8   SNAP25

2,5 kb

Association study :

SNP4

P=0.005

Fréquences alléliques
SNAP25b

Early onset Bipolar patients

SNP4

P=0.22

Late onset Bipolar patients

Expression study :

P=0.04

mRNA Expression
SNAP25b

AA+AC   CC

SNP4

⇨ 60 samples of human prefrontal cortex (BA46)

SNAP25b

○ Most frequent genotype in early onset bipolar disorder

■ Bipolar disorder

□ unaffected

Etain *et al.*, *Mol Psychiatry* 2009

Genome Wide Association studies GWAS and bipolar disorder

Genome-wide association studies of bipolar disorder

Study	Sample	Individual typing or pooled typing	Top hit (SNP, position, significance and nearest gene)	Number of independent hits at $P < 10^{-4}$
WTCCC	1868 cases	Individual typing using Affymetrix 500K array	rs420259 23.5 Mb on chromosome 16 ($P = 6.3 \times 10^{-8}$)	98
WTCCC, *Nature* 2007	2938 controls		PALB2	
STEP-BD/UCL (Broad)	1461 cases	Individual typing using Affymetrix 500K or 5.0 arrays	rs4939921 at 45.7 Mb on chromosome 18 ($P = 1.7 \times 10^{-7}$)	32
Sklar *et al.*, *Mol Psy* 2008	2008 controls		MYO5B	
Edinburgh/Dublin (Broad)	1098 cases	Individual typing using Affymetrix 5.0 or 6.0 arrays	rs7221510 at 43.7 Mb on chromosome 17 ($P = 1.4 \times 10^{-6}$)	27
Ferreira *et al.*, *Nat Genet* 2008	1267 controls		SKAP1	
NIMH/Bonn	1233 cases	Pooled genotype analysis using Illumina 550 array	rs1012053 at 41.6 Mb on chromosome 13 ($P = 1.5 \times 10^{-8}$)	3
Baum *et al.*, *Mol Psy* 2008	1439 controls		DGKH	
Meta-Analysis	4387 cases	325,690 SNPs	rs10994336 in *ANK3* on 10q21 ($P = 9 \times 10^{-9}$)	
	6209 controls		rs1006737 in *CACNA1C* on 12p13 ($P = 7 \times 10^{-8}$)	

Craddock and Sklar, *Trends Genet* 2009

GWAS of early-onset and familial cases of bipolar disorder
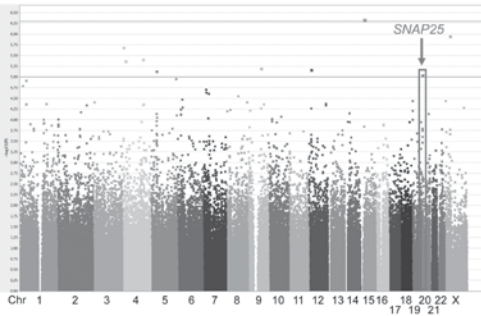
Cases:

331 patients with early-onset BP
137 familial cases of BP

468 patients
(233 French and 235 German)

Controls:
1,823 French controls
1,009 German controls
2,832 Controls

Genotyping on Infinium HumanHap500 and Humahap300 bead chips (Illumina inc.)

Common SNPs analysed for this study:
313,952 SNPs

SNAP25	rs1999552 ($P = 9 \times 10^{-5}$)
ANK3	rs1459731 ($P = 3 \times 10^{-3}$)
CACNA1C	rs4298967 ($P = 2 \times 10^{-3}$)

Jamain, Cichon, Etain et al, submitted

GWAS of early-onset bipolar disorder

$N_{cases} = 331$
$N_{controls} = 2,832$
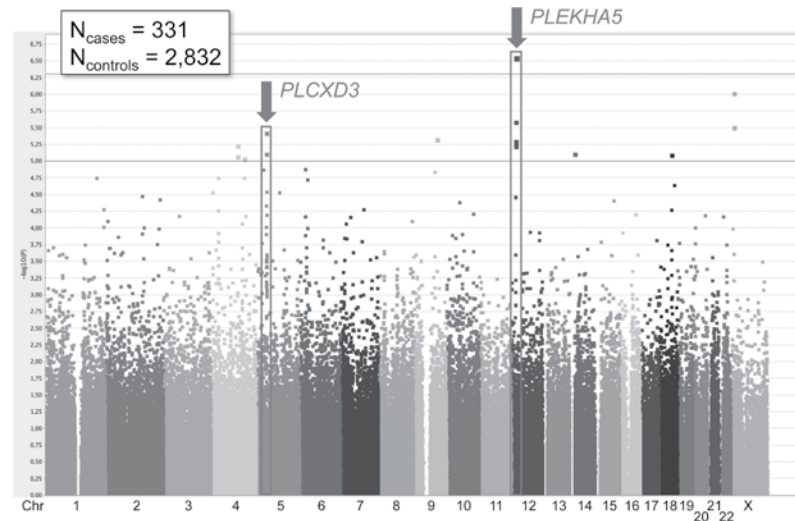
The phosphoinositide signaling pathway
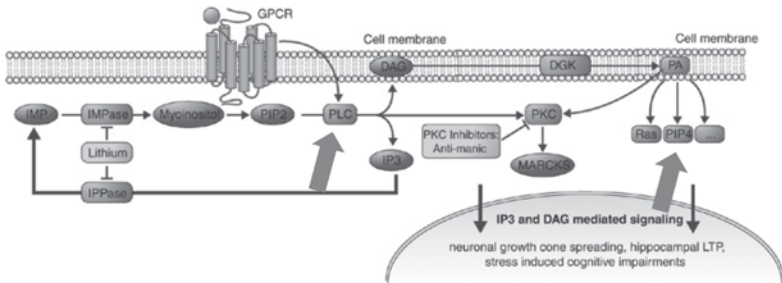
GWAs of early onset BP : Identification of two genes encoding phosphoinositide interacting proteins : *PLEKHA5 and PLCXD3*

Schloesser *et al.*, *Neuropsychopharmacology* 2008

Early-onset Bipolar disorder and neuron connectivity
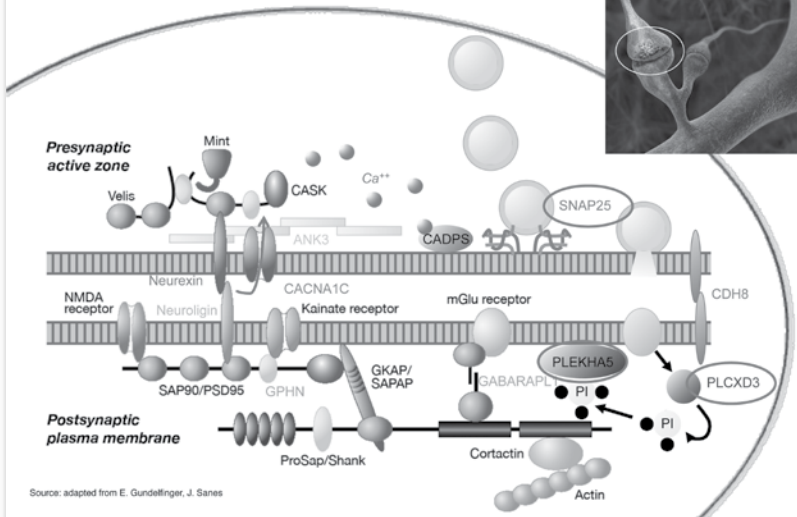
Source: adapted from E. Gundelfinger, J. Sanes

GENETIC STRATEGIES *Searching for biological pathway :*

Clock genes : candidates in BP ?
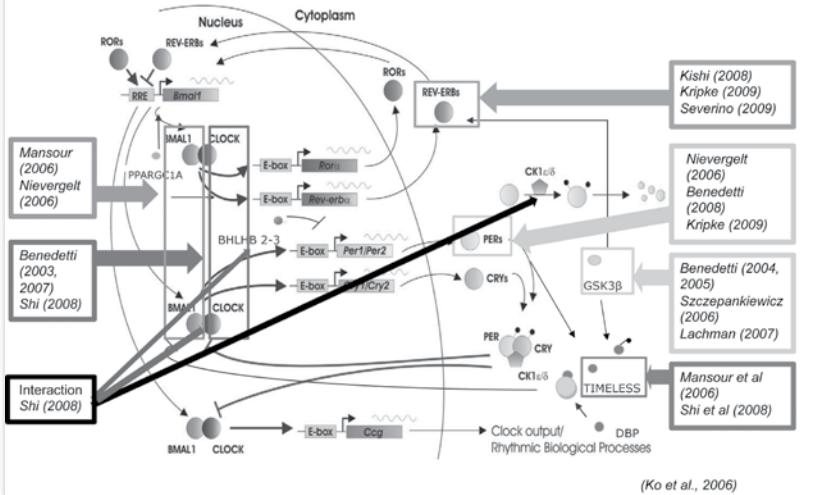
GENETIC STRATEGIES *Searching for biological pathway*

Melatonin pathway: a candidate in BP ?

The 'Hormone of Darkness'

- Synthetized in the pineal gland
- Regulated by light∕dark cycle
- Via the suprachiasmatic nucleus
- Melatonin secretion is highly heritable

Pineal Gland
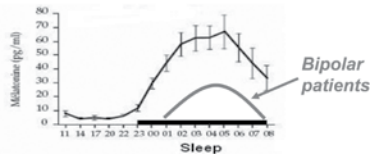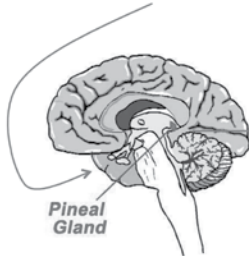
Bipolar patients

Melatonin secretion peaks at night

- Abnormal Melatonin secretion in bipolar patients

Nurnberger JI Jr 2000

- Disturbances of sleep/circadian rhythm in early onset bipolar disorder

Lofthouse 2008; Dilsaver 2009; Mansour 2005

Melatonin Biosynthesis

Serotonin

Arylalkylamine
N-acetyltransferase (AA-NAT)

←— *AA-NAT* : Rate Limiting

N-Acetylserotonin

Hydroxyindole-O-methyl-
transferase (HIOMT)   CYP2C19 (or CYP1A2)

Melatonin

ASMT

Acetyl Serotonin Methyl transferase

Associated with Autism and Asperger syndrome

- Sleep disturbances
- Circadian abnormalities
- Low melatonin levels
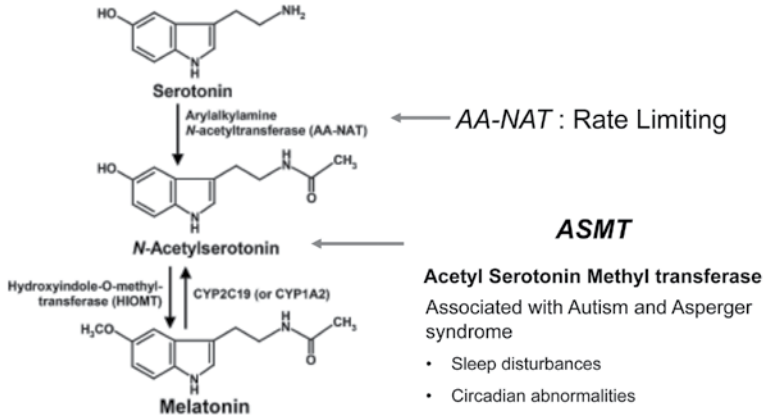
Melke J, et al. Mol Psychiatry 2008.

Rare variants of ASMT (AcetylSerotonin Methyltransferase) in 350 bipolar patients

ASMT

| BP1 | BP2 | BP3 | BP4 | BP6 | BP7 | BP8 | BP9 | BP10 |

R210H

BP5

2 bp deletion in exon 1

R111K   IVS5+2T>C   P271L   Y276H   E316D   L326F

V333M

R210H
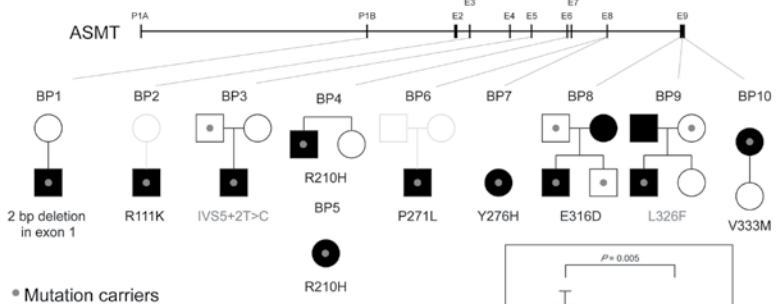
• Mutation carriers

ASMT mutations
→ 2.6% of bipolar patients
→ 8 variants not observed in controls
→ these variants are associated with low enzyme activity *(lymphoblastoid cell lines)*
→ Carriers are men, early onset BP disorder, positive family history for BP

P = 0.005

ASMT activity (pmol/min/mg)

Wild type   Mutant
N=6   N=10

Jamain et al, submitted

Association with ASMT

E2 E6
P1A E1 E3 E4 E5 E7 E8
P1B
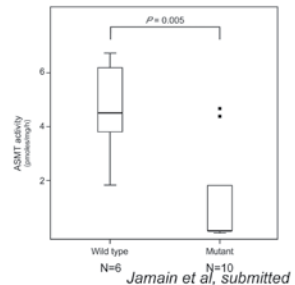
11 SNPs
308 bipolar patients and 158 controls

prom1B (promotor) and rs28675287 (intron 5)

haplotype frequency 'AT' BP > controls
($p = 0.0028$ et $p_c = 0.0057$)

'AT' associated to a diminished level of mRNA

ASMT activity diminished
in lymphoblastoid cell lines of Bipolar patients

Melatonin catabolism in pineal gland

INDO and INDOL1   chr8:39840484..40030807(190.33kb) including 50kb border

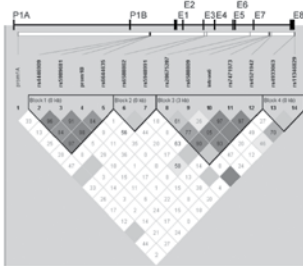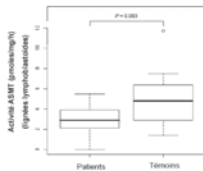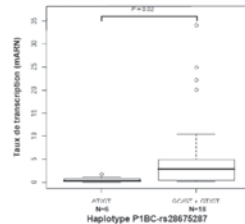| CHR	SNP	BP	A1	F_A	F_U	A2	CHISQ	P	OR
8	rs7830240	39855543	C	0.41	0.39	T	1.16	0.27	1.08
8	rs7812558	39870563	C	0.24	0.24	A	0.06	0.79	0.97
8	rs10086541	39873937	A	0.41	0.39	G	0.80	0.36	1.06
8	rs3808606	39888532	A	0.47	0.46	G	0.51	0.43	1.05
8	rs10108662	39896146	A	0.33	0.34	T	0.02	0.82	0.99
8	rs7845217	39912475	C	0.13	0.13	T	0.09	0.76	1.03
8	rs13248917	39918113	G	0.43	0.49	A	9.87	0.001	0.79
8	rs7832080	39918914	C	0.42	0.37	T	8.35	0.003	1.23
8	rs2543046	39936527	C	0.42	0.37	A	8.20	0.004	1.23
8	rs1035290	39953434	C	0.24	0.23	T	1.41	0.23	1.10
8	rs4736794	39959391	G	0.10	0.10	A	0.01	0.89	0.98
8	rs2955877	39968092	A	0.25	0.26	G	0.06	0.80	0.97
8	rs10104711	39977183	A	0.24	0.23	G	0.50	0.44	1.05
8	rs7837357	39977897	C	0.13	0.12	T	0.68	0.40	1.09
8	rs10109853	39982038	C	0.50	0.49	T	0.10	0.75	1.02
8	rs10958579	39986994	A	0.27	0.28	G	0.26	0.60	0.96
8	rs2981156	39988790	C	0.27	0.26	T	0.78	0.37	1.07
8	rs2981157	39988996	A	0.36	0.36	C	0.01	0.89	0.99
8	rs461138	39991286	T	0.13	0.15	C	2.74	0.09	0.84
8	rs2981182	40010613	T	0.43	0.44	G	0.43	0.51	0.95
8	rs4737003	40018187	A	0.08	0.09	C	2.63	0.10	0.80
8	rs5997214	40019346	G	0.39	0.37	A	1.44	0.22	1.09
8	rs2929104	40030807	T	0.36	0.37	G	0.53	0.46	0.94

melatonin

↓ indoleamine
2,3–dioxygenase
(INDO and INDOL1)

Formyl-N-acetyl-5-
methoxykynurenamine
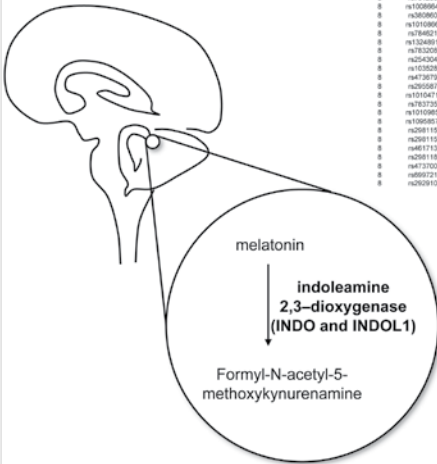
Association between INDO/INDOL1 and BP

Haplotype   rs13248917-rs7832080-rs2543046

HAPLOTYPE	F_A	F_U	CHISQ	DF	P
ACC	0.41	0.36	7.84	1	0.005
GTC	0.01	0.01	0.017	1	0.89
ACA	0.019	0.017	0.18	1	0.67
GTA	0.43	0.48	10.05	1	0.001
ATA	0.134	0.128	0.23	1	0.63

Adapted from Harvey AG. *Am J Psychiatry 2008*
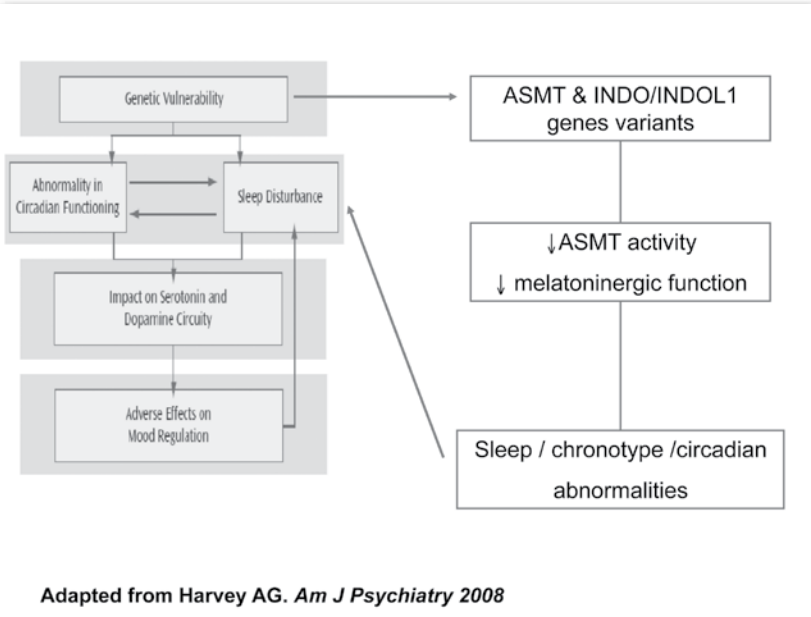
Modern Genetic strategies *and* Phenotypic Refinement are Not Enough!

Chromo-somes with established linkage	Localization of candidate genes	Adult bipolars						Early-onset		
		Badner et al. 2002	Segurado et al. 2003	Fallin et al. 2004	Middleton et al. 2004	Dick et al. 2002	Dick et al. 2003	Lin et al. 2005	Etain et al. 2006	Faraone et al. 2006
Samples	-	7 data sets	18 data sets	41 pedigrees	25 pedigrees	56 pedigrees	250 pedigrees	150 pedigrees	87 sib-pairs	58 pedigrees
1				1q32						
2					2q22, 2p16		2p13		2q14.3, 2p21	
3	DRD3: 3q13.3 GSK3-?: 3q21.1			3p22			3q23		3p14	
4					4q22	4q32 4q35				
5									5q33	
6					6q22		6q16			6q25
7									7q36	
8		8p22					8q24			
9			9p22.3-21.1							9q34
10			10q11.21-22.1		10q21				10q23	
11	BDNF: 11p13 TPH1: 11p14-15.3 TH: 11p15			11q12		11p15				
13	5-HT2A: 13q14-21 DAOA: 13q22-34	13q31								
14			14q24.1-32.12							
16					16p12	16p13			16q23	
17	5-HTT: 17q11.1-12						17q25			
18			several regions	18q22						
20						20p12			20p12	20q11
21								21q22.13		
22	COMT: 22q11	22q11-13								
X	MAOA: Xp11.12-11.4					Xp11				

3. Environmental factors in bipolar disorder ?

- **Childhood traumatic events ?**
- Life events ?
- Season of birth ?
- In utero infections ?
- Obstetrical complications ?

- ………

Etain et al, Bipolar Disorder, 2008

---

3. Environmental factors in bipolar disorder
Early Childhood trauma ?

- Childhood traumatic events : an environmental risk factor for BP
   - More frequent in BP than UP
   - History of severe childhood abuse in > 50 % BP patients

- Childhood trauma modulate the clinical expression of BPAD :
   - **Early age at onset**
   - Rapid cycling course
   - Psychotic features
   - Suicidal behavior
   - Comorbidities with substance misuse and panic disorder

Levitan et al. 1998, Brown et al. 2005 ; Carballo et al. 2008 ; Garno et al. 2005
Hammersley et al. 2003, Leverich et al. 2002 ,2003, 2006, Romero et al. 2009,Etain et al, 2010

3. Environmental factors in bipolar disorder
Early Childhood trauma ?

Childhood Trauma Questionnaire (CTQ)

- Self rating scale

- Retrospective assessment of childhood trauma

- Good face validity in comparison to interviews

- Five sub-scores (categorical or continuous)
  Emotional neglect
  Emotional abuse
  Physical neglect
  Physical abuse
  Sexual abuse

Bernstein et al, 1994.

---

3. Environmental factors in bipolar disorder
Early Childhood trauma ?

- Retrospective assessment of childhood trauma with a Self rating scale, the Children Trauma Questionnaire (CTQ)
- Five sub-scores *(Bernstein et al, 1994)*

- Bipolar patients
- Controls

Dose-effect
p<0.0001

•p<0.005

Cochran-Armitage linear test ; p < 0.0001
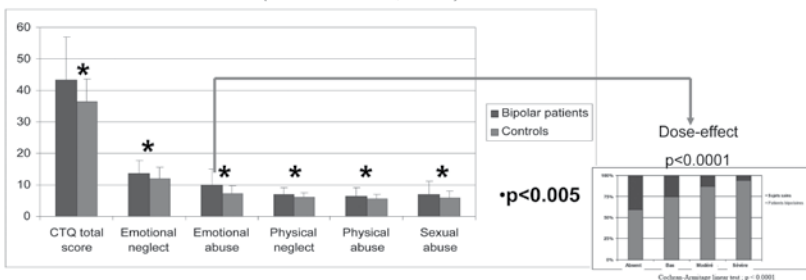
206 bipolar patients, 63 % of BP experienced at least 1 trauma
Multivariate analysis, CTQ total score p<0.0001, **Emotional abuse p<0.0001**

Etain et al, Journal of Traumatic Stress (in press)

Association study between early childhood trauma and affective dimensions in 201 BP

- Children Trauma Questionnaire (CTQ)
- Affective instability measures :
ALS (Affective Lability Scale) and AIM (Affect Intensity Measure : higher in BP
(Henry et al, Psychiatry Research, 2008)

Only emotional abuse (CTQ): associated to affective instability

ALS : X^2=0.18 p<0.0001   AIM : X^2 =0.17 p<0.0001
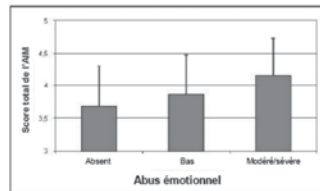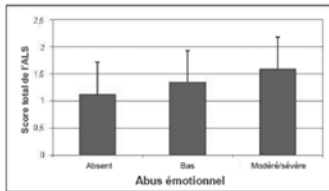
4. Gene X Environment Interactions

Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction

Avshalom Caspi, Terrie E. Moffitt, Mary Cannon, Joseph McClay, Robin Murray, HonaLee Harrington, Alan Taylor, Louise Arseneault, Ben Williams, Antony Braithwaite, Richie Poulton, and Ian W. Craig
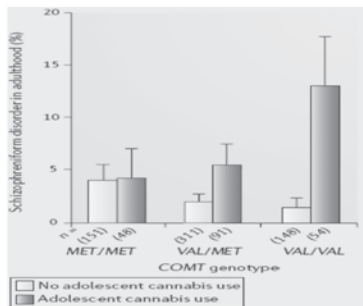
Caspi et al, Biol Psychiatry, 2005, 57, 1117-1127

Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

Avshalom Caspi,[1,2] Karen Sugden,[1] Terrie E. Moffitt,[1,2*] Alan Taylor,[1] Ian W. Craig,[1] HonaLee Harrington,[2] Joseph McClay,[1] Jonathan Mill,[1] Judy Martin,[3] Antony Braithwaite,[4] Richie Poulton[3]
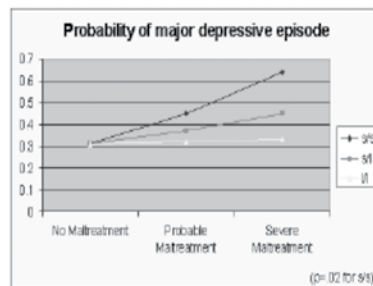
Caspi et al, Science, 2003, 301, 386-389

Correlation Between Childhood Trauma Questionnaire (CTQ) and Age at Onset (AAO) of BP Disorder
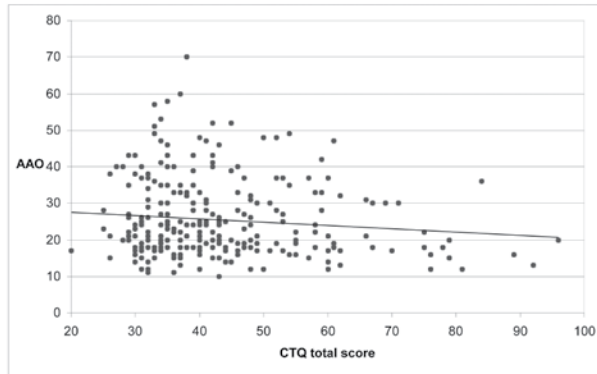
CTQ total score: beta=-0.20 p=0.05

Childhood affective trauma (CTQ), 5HTT gene and age at onset of Bipolar patients (N = 206)

Correlation between AAO and CTQ after stratification for the 5HTTLPR genotype
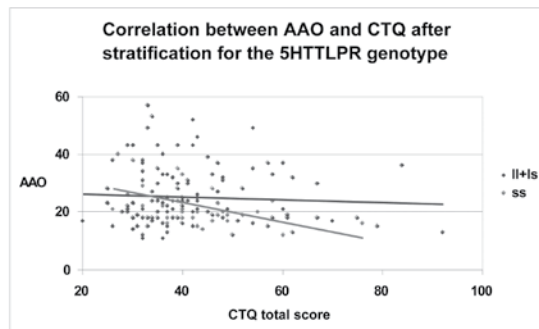
- « s » allele of 5HTTLPR more frequent in early onset BP (50.6% versus 35.7, p=0.08)

- Correlation of early trauma and age at onset is only observed only among « ss » homozygotes bipolar patients (rho=-0.51 **p=0.003**) and not among l allele carriers (rho=-0.007 p=0.94)
  Etain et al., Bipolar Disorders 2008

Genetic and Environmental risk factors in BD

1. PHENOTYPIC REFINEMENT : early onset BD disorder

- Association with ASMT and IDO = melatonin pathway
- Association with 3 genes implicated in Phosphatidyl-inositol

2. ENVIRONMENTAL FACTOR : early childhood trauma

- Associated with bipolar disorder
- Interaction between childhood trauma and candidate genes
- Emotional abuse are associated to affective instability

Etain et al. Bipolar Disorders, 2008.
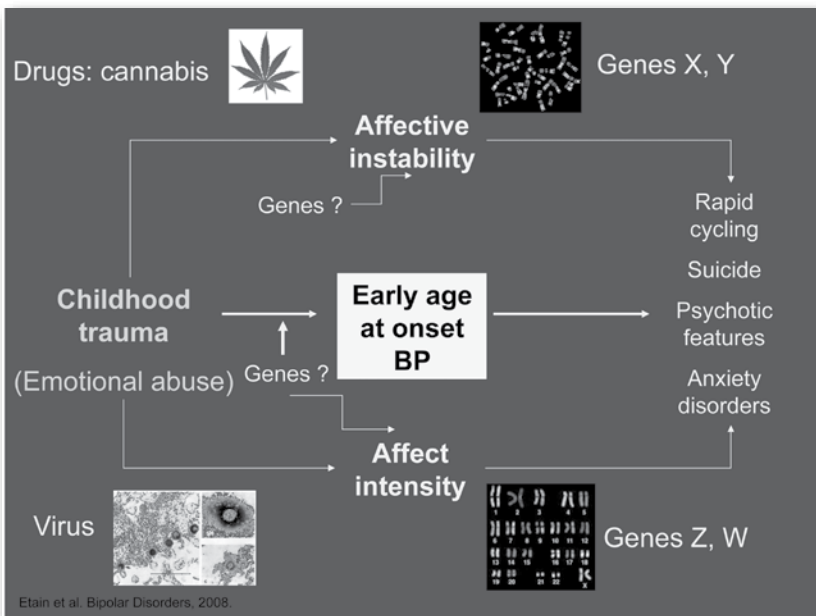
Conclusions
Identification of early onset bipolar disorder :
Implication for clinical practice

Systematic recording of age at onset of the first mood episode is important in order to identify early onset BP patients

• Systematic assessment of comorbid disorders in early onset BP
  ✓ ADHD
  ✓ Anxious disorders
  ✓ Alcohol and drug abuse
  ✓ Suicidal history

• Implications for further diagnostic criteria (DSM-V ?) and for the choice of treatment strategies (psychotropic and psycho- social remain to be clarified

Conclusions
Early childhood trauma (emotional abuse)
Implication for clinical practice

1. Systematic assessment of past childhood trauma in BP patients should be included in everyday clinical practice

2. Recognition of the role of emotional abuse in bipolar disorder may have several therapeutic implications including :
psychosocial, trauma-focused, emotional-focused cognitive therapy and pharmacotherapy
which in turn may improve the prognosis of the disorder.

3.Towards the core phenotype of BP: Identification of environmental stressors may in turn help phenotypic refinement
  ➡ the concept of abnormal emotional reactivity

Acknowledgments

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Fax: + 46 - 8 - 30 28 75
E-mail: Sven.Ove.Ogren@ki.se

Academic Background

Professor of Neurobiology, Department of Neuroscience and Neurobiology, Karolinska Institutet, Stockholm.
1999 Head of the Division of Behavioral Neuroscience, Department of Neuroscience, Karolinska Institutet, Stockholm.

Professional Credentials

1979-1990 Vice President of Preclinical Research, Senior Scientific Adviser and Senior Director at Astra Alab AB (now Astra Zeneca). Inventor and project leader of compounds launched as antidepressant and antipsychotic drugs, e.g. remoxipride and zimelidine. Holder of more than 30 international patents.

Membership of Scientific Societies

American College of Neuropsychopharmacology (ACNP)
Collegium Internationale Neuro-Psychopharmacologicum (CINP)
European College of Neuropsychopharmacology (ECNP)
Fellow, Academia, Medicinae and Psychiatriae Foundation
Chairman of the Scientific Programme Committee 2006-2009. Member of the Executive Committee of ECNP, Counselor of ECNP 2002-2005
Chairman of the Award Committee ECNP 2005-2008
Current Secretary of ECNP

Publications

Published more than 370 original papers and book chapters as well as 35 review articles. More than 200 posters and 300 abstracts have been presented at international meetings.

Guest Researchers and Graduate Students

Fifteen postgraduate students and eight graduate (PhD) students have been supervised since 1991.
Co.supervisor: M. Bäckberg (2004), A. Mattsson (2005), Linnea Asp(2009).

Prizes and Awards

Swedish American Foundation, one year scholarship at Towson State College, Baltimore, 1964.

The Hilda and Alfred Erikssons Prize, Swedish Academy of Sciences, 1995.

Oswald Schmiedeberg´s medal,Department of Pharmacology,University of Riga,Latvia,1998.

Gold medal,University of Medical Informatics and Technology, Tyrol, Innsbruck, Austria, 2004.

Honorary member of of the Austrian Society for Neuropsychopharmacology and Biological Psychiatry,Vienna, Austria, 2004.

Development of new targets for new drugs in psychiatry

Sven Ove Ögren

Karolinska Institutet, Department of Neuroscience,
Retzius väg 8, 17177 Stockholm, Sweden

There is a compelling rationale for improving treatment of psychiatric disorders such as anxiety, depression and schizophrenia which are major causes of disabily worldwide and with a huge impact on the individual and society. The discovery of novel improved treatment in psychiatry has been slow due to major challenges e.g. the pathophysiology of these disorders is not known and there is a lack of validated biomarkers and animal models. Moreover, our knowledge on brain function has mainly been based on studies with current drugs. Despite these limitations, the past two decades has witnessed a tremendous increase in the number of potential new targets for new drugs in psychiatry. This development is based on accelerating knowledge of normal brain functions and human psychopathology as well as a deeper understanding of the multiple actions of the drugs currently used to treat psychiatric disorders. The increase in knowledge has given a more detailed picture about the complex role of brain neuromodulatory systems in health and disease. Mental disorders involve multiple and partly overlapping neurotransmitter systems interacting at different levels in a number of brain networks. Brain areas important for emotional regulation, such as the limbic areas, overlap with neuronal structures controlling cognitive functions. This development has changed focus of drug discovery from action on single drug targets to multiple targets. An example is the recent development of antipsychotic drugs with combined $5\text{-}HT_{1A}$ agonism and D_2 blockade (Newman-Tancredi A., Curr Opin Investig Drugs. 2010;11(7):802-12.). Moreover, although monoaminergic targets are still pursued to a high degree, there is an increased focus on non-aminergic targets such as melatonin, glutamate modulators, cholinergic signalling mechanisms, neurotropins and to some extent neuropeptides. In addition, there are a large number of emerging targets based on findings in genetic epidemiology aimed at identifying genes associated with mental disorders and their signalling mechanisms. An example is susceptibility genes related to schizophrenia such as neuregulin (NRG1). NRG1 knockout-mice, which have a decreased NMDA-receptor expression, display a "schizophrenia-like phenotype" including cognitive dysfunctions (Rico and Marin, Curr Opin Genet Dev, 2011, Epub ahead of print). Development of relevant

animal models based on genetic and epigenetic information will be critical for identifying new therapeutic strategies. In conclusion, multiple approaches will be used to identify potential drug targets in psychiatry. The great challenge for the development of new targets will be to integrate the accelerating knowledge of human pathophysiological mechanisms in the drug discovery process.

Development of new targets for new drugs in psychiatry

Sven Ove Ögren

Dept. of Neuroscience, Karolinska Institutet

Urgent need for improved treatment for psychiatric disorders

•Psychiatric disorders such as anxiety, depression and schizophrenia are the main cause of disability worldwide.

•These disorders have a high social impact.

•A large number of patients do not respond well or at all to current drug therapies.

•Many of the current drug treatments show an unacceptable range of side-effects.

Major challenges in novel drug development for psychiatry

·Theories on brain disorders based on the mechanisms of action of current drugs discovered mainly by clinical observations, e.g. imipramine and chlorpromazine

·Limited knowledge of the underlying etiology and psychopathology.

·The diagnostic process is largely descriptive.

·The heterogenity in disease mechanisms and development

·No established biological markers for pre-clinical and clinical assessment.

·The lack of validated animal models with translational value e.g. target validation critical.

The current state of drug discovery in psychiatry

·During the past two decades, a move from action on single drug targets to multiple targets.

·Monoaminergic approaches are still pursued with focus on drugs acting on several neurotransmitter systems.

·Recent focus on truly novel mechanisms and targets such as melatonin, neurotropins, glutamate receptors, cholinergic nicotinic systems and neuropeptides.

·Emerging targets based on findings in genetic epidemiology aimed at identifying genes for common diseases (Novel gene targeted drugs).

Current pharmacotherapy of major depressive disorder (MDD)

All current drugs act via monoaminergic mechanisms

MAOI	TCA	SSRI	Receptor antagonists	SNRI	NARI	NDRI	Melatonin agonist
Phenelzine	Clomipramine Imipramine Amitriptyline	Paroxetine Fluoxetine Sertraline Fluvoxamine Citalopram Escitalopram	Mirtazapine Trazodone Mianserin	Venlafaxine Milnacipran Duloxetine	Reboxetine	Bupropion	Agomelatine
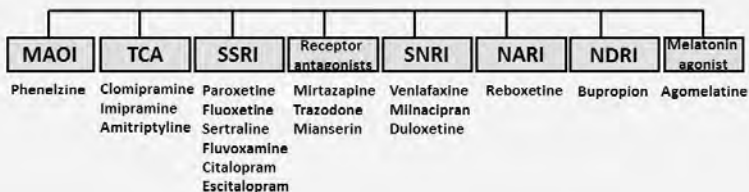
Depression (MDD): large unmet medical needs

- Current treatment: selective serotonin reuptake inhibitors (SSRI's) or selective noradrenaline reuptake inhibitors (SNRI's) or their combination.

- Onset of clinical effect within 2-3 weeks.

- About 40% of patients do not respond well or are therapy-resistant.

- The effect size is usually small in placebo studies.

- Limited short-term efficacy and their long-term profylactic efficacy remains uncertain (STAR*D project)

- A number of side-effects which cause problems with compliance.

Multiple pre- and postsynaptic 5-HT receptor subtypes

Wong et al, 2005
Nature Reviews Drug Discovery
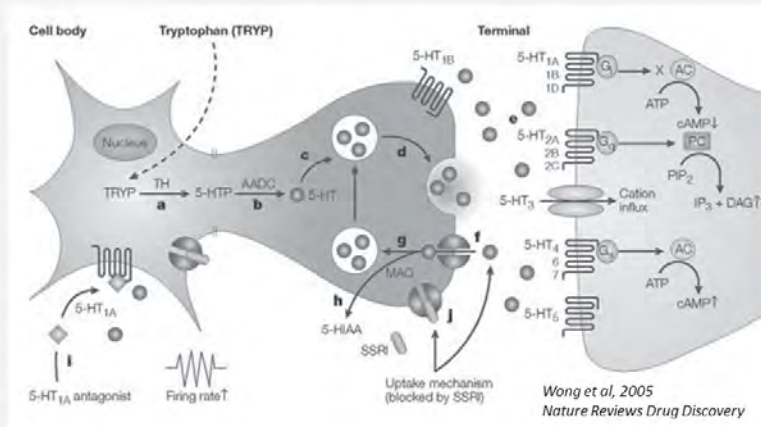
Different neurotransmitters may modulate different symptoms in depression
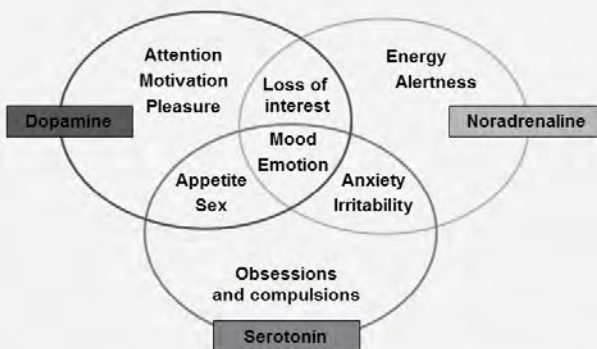
Nutt D et al.; J Psychopharmacol 2007 21:461-71

Is there a final common pathway underlying the antidepressant response?

- Delayed onset of clinical effects by antidepressant drugs have resulted in the belief that the antidepressant action, although initiated by primary effect of the compounds, involves secondary mechanisms including changes in gene expression and/or synaptic plasticity.

- A number of final common pathways have been suggested:

1. Increase in cAMP and related secondary messengers molecules, such as CREB, as a result of e.g. noradrenaline reuptake inhibition.
2. Enhancement of serotonergic activity and post-synaptic 5-HT1A receptor transmission (Chaput et al., 1991).
3. Increase in gene expression of brain-derived neurotrophic factors (BDNF), or other neurotrophic/neuroprotective factors (Manji et al., 2001; Castreen et al., 2006).
4. Attenuation of transmission of NMDA-glutamatergic receptor functions and increase of GABA receptor function (Paul and Skolnick, 2003).

Monoaminergic and non-aminergic research approaches in depression

- Triple uptake blockers (Balance 5-HT, NA, DA?)
- Agomelatine - the first melatonergic acting drug in depression. MT_1/MT_2-agonist ; $5\text{-}HT_{2C}$ antagonist.
- Combinations of SSRI and 5-HT-receptor subtypes; $5\text{-}HT_{1A}$ or $5\text{-}HT_{2C}$.
- Modulators of excitatory amino-acids, e.g. ketamine in therapy-resistant patients.
- Modulators of neurotrophins, e.g. BDNF and its receptor Track B
- Phosphodiesterase type 4 (PDE-4) inhibitors e.g. Rolipram (cAMP $\rightarrow$PKA $\rightarrow$ CREB $\rightarrow$ Antidepressant effect?).
- Neuropeptide approaches
  - NK 1 (substance P) antagonists, Aprepritant (Merck, USA) (Not persued)
  - CRH-1-antagonist. Antidepressants with anti-stress mechanisms of action have failed to demonstrate efficacy.The CRH_1 antagonists (CP-316, 311)-lack of efficacy vs. Placebo and sertaline in a 6 week trial in major depression(Binneman et al.,Am J Pychiat 165,617-620,200).

Several brain neuropeptides are involved in regulation of mood and their receptors are potential targets for novel antidepressants

Peptide receptors	Animal depression models	Non-peptidergic ligands developed
MCH$_1$	MCH$_1$ antagonists-antidepressant-like	ATC0175; SNAP-7941
NK$_1$	NK$_1$- antagonists-antidepressant-like	Aprepitant; MK0869, NK1 antagonist
CRF$_1$	CRF$_1$-antagonists-antidepressant-like	DMP696; R121919
NPY-Y1, NPY-Y2	NPY-Y1 agonists-antidepressant-like	Agonists not available
GalR3	Non-selective galanin antagonist M15-antidepressant-like GalR3 antagonists-antidepressant-like,	SNAP37899, SNAP398299
NOP	NOP receptor antagonists-antidepressant-like	J-113997

Modified from Ögren et al., 2006

Limitations of current antipsychotic drug therapy

- Need for improved efficacy on the psychiatric syndrome
- Need for efficacy in therapy-resistent patients
- Limited or no improvement of negative symptoms and/or cognitive dysfunctions
- Need for elimination of the major side-effects; EPS, metabolic syndrome, neuroendocrine disturbances, cardiotoxic effects (QT prolongation)

Relationship between D_2 affinities and clinical potency
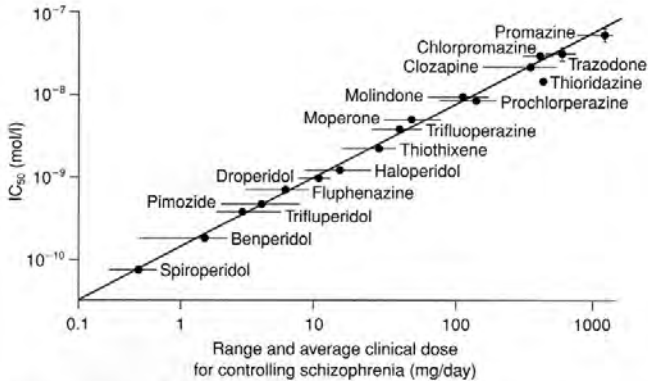
Creese et al. 1976.

Modulators of NMDA-receptor function

- A hypoglutamatergic state is caused by early (genetic or non-genetic) neurodevelopmental disturbances triggering psychosis in adulthood.

- This glutamatergic hypostate results in a disinhibition of excitatory transmission. Reduction in NMDA-receptor function on GABA, 5-HT, Ach and NA-neurons relieves glutamate from inhibition.

- This hypothesis may be modeled in rodents by NMDA-receptor blockade by phencyclidine (PCP) (Olney and Farber, 1995).

Glu

GABA

NMDA-R

Phencyclidine
↓
NMDA-receptor blockade
↓
Disinhibition of pyramidal cell
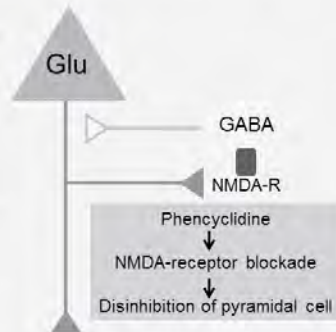
Olney & Farber, 1995

Second generation "atypical" antipsychotics

Clozapine

Olanzapine

Quetiapin

Risperidone

Ziprasidone

- Antipsychotic effects combined with relatively low EPS.
- Exhibit multireceptor actions. DA D_2 receptor blockade combined with receptors of the 5-HT family: $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$.
- Side-effects, including metabolic dysfunction and weight gain, related to interactions with noradrenergic alpha$_1$, muscarinic M_1 and M_3, serotonin $5\text{-}HT_{2C}$ and histamine H_1 receptors.

New trends in antipsychotic pharmacotherapy: "The third generation of antipsychotic drugs"

Aripiprazole

Bifeprunox (not developed)

Perospirone (marketed)

Lurasidone (approved by FDA)

- Combine preferential agonist (or partial agonist) activity at DA D_2 with partial agonist action at $5\text{-}HT_{1A}$ receptors.
- Little interaction with receptor sites involved in side-effects, e.g. muscarinic$_2$ receptors in animal models
- Low EPS potential while being active in animal models of schizophrenia. Potential improvement of negative symptoms and cognitive impairments

Newman-Tancredi., Curr Opin Investig. Drugs, 802-812, 2010.

Emerging targets in schizophrenia

1. Effects on glutamatergic signaling, Agonists and metabotropic receptors, mGluR2/3-agonist (Paul et al., Nat.Med. 13, 1102-1107, 2007). Development of metabotropic 2/3 agonists for schizophrenia. These compounds will in principle reduce glutamatergic release due to stimulation of presynaptic metabotropic receptors.A recent Phase 2 clinical trial with the mGlu2/3 agonist LY404039 has shown statistically significant effects on positive and negative symptoms at week 4 comparable with olanzapine. (Putil et al., Nat. Med. 2007, 13 (1102-1107) is selective targeting of the Glu2/3 receptor of mechanisms for antipsychotic efficacy?

2. Modulation of GABAergic signaling MK-0777, on allosteric modulators of the $GABA_A\alpha_2$receptor (Lewis and Moghaddam, Arch Neural 63, 1372-1376, 2006). Disturbances in parvalbumin expressing GABA-neurons contributing to impaired synchronization of pyramidal cells.

3. Cholinergic nicotinic receptor signaling.
   $(\alpha_4)_2(\beta_2)_3$- post- and pre-synaptic excitation of Na^+ and K^+ permeability.
   $(\alpha_7)_5$- post- and pre-synaptic excitation of Ca^{2+} permeability.
   Deficits in the expression and function of $\alpha_2\beta_4\alpha_7$-nicotine receptors are found in
   schizophrenic brains may be responsible for the auditory deficit seen in schizophrenic patients.
   Diminished suppression of an auditory-evoked response (p50) to repeated stimuli has been related to
   learning problems in schizophrenic patients (Freedman et al., 1997).
   Blockade of the α_7-receptor causes sensory gating deficits as seen in schizophrenia (Luntz-Leibman et al., 1992)

A number of approaches are currently used to alleviate cognitive dysfunctions in schizophrenia

	clozapine	olanzapine
5-HT$_{1A}$ antagonism/agonism	√	√
5-HT$_2$ antagonism	√	√
5-HT$_6$ antagonism	√	√
Dopamine increase (cortex). DA D$_1$receptor activation	√	√
Acetylcholine increase or nicotinic agonists (cortex/hippocampus)	√	√
Glutamate increase? (cortex)	√	√
Muscarinic agonism/antagonism, M$_1$receptor agonists	√	√
Histamine-H$_3$ antagonism	?	?

Molecular target in schizophrenia based on disease gene identification

- Candidate genes
    - Genes are selected on the basis of their "known" function
    - Drawbacks
        - Selection based on A priori hypothesis and not genome wide
- Genomewide association studies (GWAS)/positional cloning
    - Chromosomal location is used to identify genes related to the disorder
    - Linkage-cosegregation in families with the disorder
    - Association- Assessment of allele frequencies in populations
    - Advantadges and disadvantadges
    - New genes can be found but specific genes can be missed.
- Mapping studies have identified a large number of genes associated with mood disorders and schizophrenia.

Disc1=disrupted in schizophrenia

NRG1=Neuroregulin1

COMT= Catecholamine-O-methyl transferase

(see Genomewide Association Studies: History, Rationale, and Prospects for Psychiatric Disorders., Am J Psychiatry 166:5, 540-556. 2009).

Summary

• To better define the neurocircuitry and molecular mechanisms of mental disorders is critical for further progress

• The underlying impairments in psychiatric disorders are heterogenous indicating the need for multiple measures of neurobiological correlates

• There is need for better and validated animal models based on genetic information which mimic affective and cognitive domains of psychiatric disorders

• These models can assist in drug development if they are able to incorporate genetic environmental interactions

Jaanus Harro, MD, PhD

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Jaanus Harro received the degree of Candidate of Medical Sciences in Pharmacology at the University of Tartu in 1990, and Doctor of Medicine in Medical Pharmacology at the University of Uppsala in 1993.

Currently Jaanus Harro is Professor of Psychophysiology at the University of Tartu, and Director of the Estonian Centre of Behavioural and Health Sciences. He has contributed to psychopharmacology of anxiolytic, anxiogenic, and antidepressant drugs and neuropeptides, developed animal models of human psychopathology, and studied molecular genetics of affect in humans. Jaanus Harro has published about 150 papers in major journals and book chapters, and supervised sixteen completed PhD dissertations in medicine, psychology and biochemistry.

Jaanus Harro is member of Collegium Internationale Neuro-Psychopharmacologicum, European College of Neuro-Psychopharmacology and Society for Neuroscience. Currently he serves as a member of the Executive Committee of the ECNP, and is a Field Editor of "European Neuropsychopharmacology". Jaanus Harro is also a member of the Estonian Society of Pharmacology, the Estonian Union of Psychologists and the Estonian Association of Psychiatrists, also serving as the chairman of the Biological Psychiatry Section of the latter. He has received the National Science Prize in Medicine (2005) and the Order of White Star Class IV.

Alexander Zharkovsky, MD, PhD

Professsor Alexander Zharkovsky (MD, PhD, D.Sci) is Head of the Department of Pharmacology at the Medical Faculty University of Tartu, Estonia. He is also a member of the Centre of Excellence for Translational Medicine at Tartu University.

Professor A. Zharkovsky has got training at Psychopharmacology Research Unit, UMDS, Guy's Hospital, London University, UK (Wellcome Trust Research Fellowship), at the Division of Pharmacology, Department of Pharmacy, Helsinki University, Finland (Sigrid Juselius Foundation Research); Fellowship at the Department of Drug Dependence Research, Karolinska   Institute, Stockholm, Sweden (Wenner Green Foundation Fellowship).

Professor Alexander Zharkovsky's areas of research: The roles of apoptosis and authophagy in the mechanisms of neuronal death; the mechanisms of brain plasticity in the psychiatric disorders and neurodegeneration, genetic animal models of psychic disorders. He is author of more than 100 scientific publications. He is supervisor of 14 PhD thesis. He participated in several international projects including EU IV, VI, VII Framework international projects as well as several domestic projects. Professor Zharkovsky has awarded Estonian Republic Award in Biomedicine 2001; Honorary Member of Latvian Pharmacological Society 2001; Medal of St Petersburg Medical University 2002.

A. Zharkovsky is a member of several international societies (British Psychopharmacological Society; Eur. Society on Biomedical Research of Alcoholism; Estonian Pharmacological Society etc), European Scientific foundation INTAS program evaluator, reviewer of several papers for the J.Neurosci, Neurosci, Brain Research.

Kaire Aadamsoo, MD

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Kaire Aadamsoo studied medicine 1987-1993 in Tartu University (TU); she continued her education for 2 years in TU postgraduate training in anaesthesiology and intensive care and for 3 years in TU residency training in psychiatry. Since 1999 she has been working in Tallinn Psychiatric Hospital, first as Head of Psychogeriatric Department, then as Psychiatrist in-chief of Psychiatry Clinic of North Estonian Medical Centre Foundation; since 2005 she has been Head of Psychiatry Clinic of North Estonian Medical Centre Foundation. NEMC Psychiatry Clinic is the largest Psychiatric clinic in Estonia with hospital of 230 inpatient beds in 8 departments, outpatient clinic and forensic psychiatry unit. Hospital includes departments of acute psychiatry, integrative treatment of first episode psychosis, neurotic and depressive disorders, acute non-psychotic crises, child psychiatry and psychogeriatry. From 2004 Kaire Aadamsoo is the vice president of the Estonian Associaton of Psychiatrists.

Erika Saluveer, MD

Head, First Episode Psychosis Department

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Erika Saluveer received her MD from Tartu University in 1984 and continued her studies as an intern in Psychiatry Clinic of Tartu University. Since 1985 Erika Saluveer has been working in Psychiatry Clinic of North Estonian Regional Hospital. She started from the outpatient department, continued in the inpatient department and from 1999 has been the Head of the First Episode Psychosis Department. Erika Saluveer is interested in psychotherapy and over the years has received broad education in this field. She works as half- time private psychotherapist from 1994. Dr. Saluveer has participated in several clinical trials in schizophrenia and mood disorders, she is teaching post-graduated students in psychiatry.

Erika Saluveer has wide clinical experience in psychosis and her department is using different innovative approaches in the diagnosis and treatment of schizophrenia.

Erika Saluveer is a member of the International Psychoanalytic Association, Estonian Associaton of Psychiatrists, Estonian Medical Association and Estonian Psychoanalytically Oriented Society.

Papers of the participants

Aet Alttoa

Department of Psychology, University of Tartu

Better understanding of the neurobiological sources that underlie and mediate the inter-individual differences in anxiety and affective states could reveal the substrates for vulnerability, elucidate the pathogenetic mechanisms, and help devise novel strategies for more effective and personalized treatments. The aim of the present study is to perform a combined analysis of the genome-wide microarray data in three different rat models of vulnerability to anxiety and depression that could identify commonalities in genes and molecular processes that underlie depression-like behaviour in these animal models. The results of this bioinformatic analysis will be presented and discussed.

Anu Aonurm-Helm

Department of Pharmacology, University of Tartu

We investigated the levels of SERT, pCREB and pTrkB in the mice with disturbed brain plasticity and depression-like phenotype, NCAM-deficient mice. We found that in these animals the SERT density and the levels of pCREB and pTrkB are dramatically reduced in frontal cortex and hippocampus in NCAM-deficient mice compared to their wild-type littermates. Interestingly, known antidepressant amitripyline was able to rescue all reductions seen in those animals, furthermore it also acted in wild-type mice. We concluded, that depressive phenotype observed in these animals at least partly can be explained by reduced levels of SERT, pCREB and pTrkB.

Olga Bragina

Department of Gene Technology, Tallinn University of Technology

The aim of this study was to investigate the effects of chlorobenzothiophene-containing molecule in neurogenesis and neuronal survival in in vitro and in vivo models.
Our in vitro experiments showed that SAG induces increased expression of Gli1 mRNA. In vitro experiments also demonstrated that SAG induces proliferation of neuronal and glial precursors without affecting the differentiation pattern of newly produced cells. Also, SAG did not

induce neurotoxicity in neuronal cultures. The SAG and Shh treatment also promoted the survival of newly generated neural cells in the dentate gyrus after their intracerebroventicular administration to adult rats.

Diva Eensoo
Department of Public Health, University of Tartu

Male subjects (n=560, Mage= 43±11,3 years) filled in questionnaires for drivers. Scales of Violations, Errors and Anger were obtained. According measured plMAO activity subjects were divided into low and medium/high plMAO activity groups. By NOS1 ex1f-VNTR subjects were divided as subjects carrying S allele and L/L genotype subjects. Subjects carrying S allele had higher scores in Violations and Errors if they had low plMAO activity compared to subjects with medium or high plMAO activity. But L/L genotype subjects had higher scores in Anger if they had low plMAO activity compared to subjects with medium or high plMAO activity.

Rauno Einula
Psychiatry Clinic, North Estonia Medical Centre

A 51 years old male patient were hospitalized at the beginning of 2011. His wife called the emergency because the patient`s behaviour was inadequate (hadn`t slept several nights, firmly nervous, dysphoric, emotionally labile) and mainly impulsive (had taken sleeping pills with a large amount of alcohol). The patient tried to explain the weird behaviour (stressful times, sleeplessness, fatigue, several somatic symptoms (urine incontinence, refluxes, hypersalivation, convulsions, diarrhoea etc.), used alcohol to put himself asleep, interestingly he complained that after the car crash (2009) alcohol hasn`t had a sedative effect for him anymore). At the beginning of 2010 he used Seroquel regularly for 3-4 months, then he decided to lower the dose step by step. According to his wife the behaviour has significantly changed after the car accident (2009).
Q: A suitable diagnose?
Q: Could it be a developing organic personality disorder (MRT was made in 2009, founded two nonspecific lesions in the frontal lobe cortex)?
Q: Is Seroquel the right drug for him? (The plus and cons of the treatment?)

Triin Eller
Department of Psychiatry, University of Tartu

To date, a number of studies have explored the effects of antidepressants on serum cytokine concentrations in patients with depression. Micova et al (2001) detected an association between higher serum IL-2R and non-response to treatment with antidepressants. Our study sample consisted of 100 outpatients with Major Depressive Disorder. We also recruited a control group of 45 healthy subjects matched by age and sex. The patients were treated with escitalopram 10-20 mg/day for 12 weeks. At the end of week 12 the patients were defined as responders if the decrease in MADRS total score was at least 50% and as remitters if the score was less than 12. Patients who did not meet these criteria were defined as non-responders. The blood samples were taken prior to and after 4 and 12 weeks of treatment. The responders showed lower baseline TNF-□ level in comparison to non-responders or healthy subjects, whereas two last groups did not differ between each other.

Kelli Hiio
Department of Psychology, University of Tartu

Personality traits play an important role in the development of psychiatric disorders. These traits are found to be genetically determined and many efforts have been made to find out genes responsible for psychiatric disorder-related traits. However successful replications are limited. My research focuses on the effects of widely studied genetic polymorphisms (5-HTTLPR, BDNF Val66Met and COMT Val158Met) on personality traits in a population representative sample (N=1176), which provides the opportunity to assess these gene effects in a large sample with very good representativeness of the general population.

Irja Ivarinen
Psychiatry Clinic, North Estonia Medical Centre

Clinical case:
ALEKS, 17 years old boy.
Lives with his mother in Tallinn. Father is spanish, lives in Spain. Parents have never lived together, but have met regularly.
First time Aleks visited child psychiatrist in spring 2008. Mother was worried about his worsened academic capacity, despite his efforts. Aleks

studied in secondary school and he suceeded well until spring 2008. At same period Aleks became more isolated, lost social internest. By the information from mother Aleks had prefered to play alone not in group already in childhood, he had never had very close friends, he had many stereotyped movements and his thinking was quite stereotyped. Psychiatrist diagnosed him Asperger`s syndrome.

First time Aleks was hospitalized in november 2008 (he was 14 years old), because of psychotic state. He had hallucinations: voices, which he believed to belong to his neighbours. His functioning was impeded by the hallucinations, because sometimes he was anxious and frightened of them, sometimes these voices were pleasant and Aleks was irritated when mother tried to stop him to speak with them. Aleks`s geit and voice had become different, he walked his back or side ahead , his voice became shrill.

In the cognitive functioning measurement were apparent marked inattentiveness, poor concentration and disturbed thinking process. Psychiatrist diagnosed him acute psychotic episoode (F23.8) and Asperger`s syndrome. He was treated with risperidone, 1 mg per day. He continued the treatment with risperidon for 7 months (december 2008 – july 2009), 1.5 mg per day. Hallucinations disappeared, but his functioning did not improve, he was engaged in autistic experiences that seriously delimit his concentration and orientation to the surroundings, emotionally he appeared distant and purposeless, was preoccupied with peculiar activities (wrote his teachers´ names, streets` names on a paper in very stereotyped way, took random buses through the city late in the evening). He was not able to continue his studies. He was concerned and anxious about his inability to study, to alleviate anxiety he received an antidpressant, sertraline 50 mg per day (january 2009 – june 2009) added to risperidone.

In summer 2009 was Aleks in Spain with father and grandparents, who were concerned about his peculiar activities. They tried to socialize him, they hid away all papers and pencils to impede him write his notes. Aleks became irritated and violent (he hit grandmother) and was hospitalized there. After the care in hospital he continued the treatment with the next medications: Abilify 15 mg, Gabapentin 800 mg, Seroquel prolong 300 mg and Fevarini 100 mg per day. He put on weight about 8 kg, he became more apathetic, isolated and emotionally withdrawn then before. Aleks thinking was seriously derailed and internally inconsistent. He continued the treatment with Seroquel prolong 300 mg per day.

In autumn 2009 he hanged the school, started to study by more individual programm, but he did not succeed well. Aleks had serious attention problems, memory impairment and difficulties in abstract thinking. After 2 months treatment with Seroquel prolong 300 mg per day Aleks mental state worsened, he had like short (2-3 days) psychotic episodes:

he believed that teachers from his prevoius school are watching for him, his neighbours intend something against him, he was afraid to leave the home, he begged mother to move away or to call the police to protect him, he was anxoius and frightened, tearful.

He received different medications, as Seroquel 600 mg per day, Abilify 30 mg per day and Serdolect 20 mg per day, but without significant improvement. In may 2010 psychiatrist diagnosed him schizophrenia (undifferentiated form).

At present Aleks has remarkable cognitive deficits (he is not able to follow educational programm for mentally retarded persons), he is severly absorbed with autistic experiences, he has short psychotic episodes (hallucinations and delusions are fragmented) and he has become violent (he has attacked his mother and grandmother for several times), he is not aware of his illness. In september 2010 he continued the treatment with Leponex, at present 100 mg per day.

Margus Kanarik
Department of Psychology, University of Tartu

Brain regions involved in vulnerability to depression

Human depression and personality traits facilitating depressogenesis can be modelled in rodents by chronically applying environmental stressors to animals previously selected for vulnerability traits. Cytochrome oxidase histochemistry, an indicator of the neuronal long-term energy metabolism, can be used to determine the brain regions involved in depression. In this analysis data from several experiments using chronic stress and vulnerability-phenotypes is collapsed to determine the brain activity pattern shared by aversive conditions and traits. The results suggest involvement of hippocampus, anterior thalamus, ventral tegmentum, median raphe, inferior colliculi, cerebellum and pons in vulnerability to depression.

Karin Kannel
Multiple Sclerosis Centre, West Tallinn Central Hospital

Case report.

82-year-old woman presents to neurology department in november 2009 with complaints of auditory hallucinations and progressive memory loss in the last 1,5 years. Bloodtests, MRI and interictal EEG with normal findings. Temporal lobe epilepsy with auditory symptoms suspected, because of patients history of secondarily generalized seizures during young

adulthood. Initially also Alzheimer's disease is diagnosed and treatment with donepezil prescribed.

Antiepileptics reduce seizures, but cognitive decline progresses rapidly within next 6 months. Later revealed that in march 2010 was diagnosed with cervical cancer and surgically treated. MRI and CSF normal, onconeural antibodies negative, but that does not exclude the possibility of paraneoplastic process. Methylprednisolone pulse therapy conducted with significant positive effect, supporting the diagnosis of paraneoplastic limbic encephalitis.

Paraneoplastic limbic encephalitis is one of the corticosteroid responsive encephalopathies. May often be initially misdiagnosed as Alzheimer's disease. Epileptic manifestations typically with temporal onset.

Evelyn Kiive
Department of Psychology, University of Tartu

The research project aims of understanding the functional consequences of previously associated genes in ADHD with focus on interaction between genes and environment in population. Gene x environment interactions on ADHD symptom related outcomes such as education and occupational choices will be examined. The sample consists of large longitudinal population representative database of 1176 subjects in two cohorts. ADHD symptom ratings were obtained from teachers at ages 9, 15 and 18. At age 25, subjects of older cohort filled in the self-report scale of ADHD for adults. Data of life events and family environment were self-reported at each study wave.

Linda Klimaviciusa
Department of Pharmacology, University of Tartu

Prolyl endopeptidase (PREP) is a cytosolic serine protease which is highly enriched in brain. PREP ihibition could be an important target for neuroprotection due to ability of PREP to cleave neuropeptides involved in learning and memory. But still there is no clear explanation, what exactly is the contribution of PREP activities to the neurodegeneration. We hypothesize that PREP could be involved in neuroinflammation, through the cleavage of anti-inflammatory peptide thymosin beta 4 (Tbeta4) in neurons and/or microglial cells. Clarifying the role of PREP in neuroinflammation will contribute to finding of new targets in neurodegeneration and neuroinflammation treatment.

Kadri Kõiv
Department of Psychology, University of Tartu

On the basis of rats' activity in a novel environment (exploration box), two clusters with stable behavioural profiles emerge: rats with high neophobia/low motivation and low neophobia/high motivation (LE- and HE-rats, respectively). Previously we have found profound differences in expression of several genes coding for major neurotransmitter systems (e.g., GABA, serotonin) in brain regions relevant for affect regulation and also differing regulation of midbrain DA-ergic and forebrain 5-HT-ergic neurotransmission in LE- and HE-rats. The presentation focuses on the question whether it is possible to change the persistent low exploratory phenotype. Two treatments are used in order to tackle the combination of low motivation and high anxiety. Preliminary results will be presented and discussed.

Kerstin Kõiva
Psychiatry Clinic, North Estonia Medical Centre

Clinical case of child psychiatry, treatment dilemma
A boy (8y) has two different diagnoses – autism spectrum disorder (Asperger syndrome) and ADHD. The behavior is restless and extremely hyperactive and includes verbal and physical aggression toward others, including mother. Without any treatment he disturbs class and is often suspended. We have tried different medications (metylphendate, neuroleptics, antidepressant). Best effect occurred by combination of metylphendate and aripiprasole. This medication combination is difficult to use as the medications cause side-effects (nausea, vomiting, loss of appetite). The side effects are problematic as the symptom of pervasive disorder causes considerable selectiveness of food.

Gerly Kukk
Department of Psychology, University of Tartu

COMT Val158Met predicts emotional valence ratings of a happy facial stimulus
Several studies have shown that COMT Val158Met has an effect on visual emotion processing and emotional awareness. The current study confirms some previous findings and demonstrates that COMT Val158Met homozygosity is related to higher negative valence ratings for the happy

facial stimulus compared to heterozygotes (one-way ANOVA; F=8,9, p<0,001). This result was statistically robust: linear regression analysis confirmed the results – COMT Val158Met was better predictor of the happy face valence scores than gender and EPIP-NEO personality traits. The results suggest that too high or too low catechol-O-methyltransferase activity might contribute to the „negativity bias".

Triin Kurrikoff
Department of Psychology, University of Tartu

If no direct gene-illness association in genetic research is found, an association might reveal after including environmental conditions in the analysis. In addition, Uher et al (2010) found, that it is important to separate objective evidence from brief self-report measures in assessing environment. Therefore, we should expand our knowledge in assessing environmental factors in gene-environment interactions. While gender often plays an important role in gene-environment studies, we should study if different environmental conditions result in different outcome among males and females in gene-environment studies. This will be an aim of my research project.

Mari-Liis Laanetu
Psychiatry Clinic, North Estonia Medical Centre

In collaboration with Tallinn University of Technology our group intends to examine the effect of electroconvulsive therapy on brain neurophysiology in depressive patients. We are interested to find out if they are related to stimulus parameters (pulse width, frequency, duration) and electrode placement (bilateral vs right-unilateral) selection. We also intend to examine the effect of ECT on cognitive functions, changes in gene-expression. Our aim is also to find out if some of these changes persist over for longer period (6 months).

Kariina Laas
Department of Psychology, University of Tartu

NOS1 gene ex1f-VNTR polymorphism influences alcohol consumption in humans

Neuronal nitric oxide synthase (NOS1) gene promoter polymorphism

ex1f-VNTR influences impulsivity-related both traits and psychopathology; impulsivity is linked to alcohol consumption. In a population based sample of young adults surprisingly not the Short risk-allele but the Long allele carriers had their first ½ standard drink at earlier age compared to SS genotype. The total alcohol consumption was higher in L-allele carriers also after controlling for impulsivity. The novel finding suggests that in alcohol consumption research the risk allele is L opposed to S-allele and the effect does not depend on impulsivity.

Helena Lass
Psychiatry Clinic, North Estonia Medical Centre

Case report: 35y old man, hospitalized 3-rd time during life. Presenting with inadequate and manic behaviour, delusional thoughts and mild cognitive impairment. Following a year in remission, psychosis relapses after stopping AP drug. Patient is also suffering from Gilbert`s syndrome. Some studies have demonstrated higher prevalence of schizophrenia in people with Gilbert`s syndrome and higher levels of neonatal UCB. Hyperbilirubinaemia has been associated with biological riskis for neurological abnormalities. During adult years patients GS has been asymptomatic. It is a matter of debate in what degree GS is contibuting to his psychotic illness and to differentiate between possible diagnoses.

Margus Lõokene
Psychiatry Clinic, North Estonia Medical Centre

In collaboration with Tallinn University of Technology our group intends to examine the effect of electroconvulsive therapy on brain neurophysiology in depressive patients. We are interested to find out if the changes in neurophysiology are related to stimulus parameters (pulse width, frequency, duration) and electrode placement (bilateral vs right-unilateral) selection. We also intend to examine the effect of ECT on cognitive functions, changes in gene-expression. Our aim is also to find out if some of these changes persist over for longer period (6 months).

Teele Nimmerfeldt
Psychiatry Clinic, North Estonia Medical Centre

A 49-year-old man with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy)
A 49-year-old man has had for the last two years migrane with aura. It started with sensory aura symptoms lasting from 30 minutes to a couple of hours followed by a headache. During the last six months he has noticed mood disturbances, cognitive impairment which has been progressive. Many relatives of his father have had subcortical ischaemic events and ischaemic strokes in their mid ages and died before the age of 70. MRI showed white-matter lesions. By genetic testing disease get confirmed, there were found mutations of the NOTCH 3 gene of chromosome 19.

Anu Planken
Research and Development, North Estonia Medical Centre

Neurotrophic factors play a role in drug addiction, which can be considered as a form of neuronal plasticity. Repeated administration of addictive drugs leads to biochemical and morphological alterations including increased expression of TH, dopamine and glutamate receptors in the dopamine neurons of the ventral tegmental area (VTA) and their target neurons in the nucleus accumbens. Glial cell line-derived factor (GDNF) has been characterized as one of the central players in the neuroadaptive processes related to addiction. GDNF inhibits the rewarding effects of drugs by blocking molecular and cellular neuroadaptive processes related to addiction. It has been demonstrated that chronic drug exposure inhibits endogenous activity of GDNF in the VTA leading to sensitized responses to subsequent drug administration.

Karita Raudkivi
Department of Psychology, University of Tartu

Glutamate transporter inhibitor PDC effect on striatal basal glutamate levels in HE/LE-rats
During exploratory behavior increase of glutamate levels have found to take place in striatum, which is presumed to be involved in stress response. It has also been shown that there are differences in basal extracellular glutamate levels of striatal glutamate in an animal model based on inter-individual diferences (high (HR) and low (LR) locomotor re-

sponse (to novel environment) model).

Therefore we investigated glutamate transporter inhibitor PDC effect on striatial glutamate levels in our HE/LE-rat model. While no baseline differences in extracellular glutamate levels were found in striatum between LE- and HE-rats, significant differences emerged after inhibition of glutamate uptake by PDC. The increase in extracellular glutamate levels induced by PDC was much higher in HE-rats compered to LE-rats. These results may help to understand the role of glutamate in anxiety-related behaviour.

Reet Reinart

Department of Bioorganic Chemistry, Institute of Chemistry, University of Tartu

G-protein coupled receptors (GPCRs) remain hot drug targets for psychiatric and neurological diseases. They comprise a large family of transmembrane proteins involved in regulation of signal transduction through the cell membrane in response to various extracellular stimuli. The focus of our research is elucidating the role of G-protein coupled receptors (GPCR) in neuroscience and reproductive medicine. Expressing proteins of choice in various cell cultures has allowed us to develop new in vitro model systems for studying receptor binding and signaling.

Teelia Rolko

Psychiatry Clinic, North Estonia Medical Centre

Borderline personality disorder, how to move on?

Objectives: an case study about 30years old male who suffers on Borderline personality disorder and co-morbid cannabis misuse Aim: there are 3 main goals of this study: first to confirm the diagnosis, secondly find out possible best psychopharmacological and psychotherapeutic interventions for the patient and thirdly to find out patient's coping strategies between the periods of hospitalization Material and Methods: to analyse previous medical history reports and current hospitalization Discussion and results: patient was at age of 10 when he first attempted suicide. There have been several hospital admissions with limited effect on improving his mental health. However, patient managed to cope long periods of time (each approx. 4year interval) without psychiatric help. Conclusions: Borderline personality disorder is challenge for the doctor as well as for the patient. Integrative treatment approach would be possibly best solution to manage this disorder.

Irina Sahnjuk
Psychiatry Clinic, North Estonia Medical Centre

Case report: 35y old man, hospitalized 3-rd time during life. Presenting with inadequate and manic behaviour, delusional thoughts and mild cognitive impairment. Following a year in remission, psychosis relapses after stopping AP drug. Patient is suffering also from Gilbert`s syndrome. Some studies have demonstrated higher prevalence of schizophrenia in people with Gilbert`s syndrome and higher levels of neonatal UCB. Hyperbilirubinaemia has been associated with biological riskis for neurological abnormalities. During adult years patients GS has been asymptomatic. It is a matter of debate in what degree GS is contibuting to his psychotic illness and to differentiate between possible diagnosis.

Katrin Sonn
Department of Pharmacology, University of Tartu

My study subject is the therapeutic potential of drugs modulating neuro-inflammation and adult neurogenesis in the prevention and treatment of Alzheimer's disease (AD). AD is characterized by progressive deterioration of cognitive functions and profound histopathological changes in the brain. Employing 5xFAD transgenic mice as a model of AD, my aims are
To study the role of microglial activation in neurodegeneration
To study the role of peripheral immunity in neuroinflammation
To study the role of brain plasticity in cognitive decline
To test the therapeutic potential of substances modulating neuroinflammation and adult neurogenesis

Merit Tõnspoeg
Psychiatry Clinic, North Estonia Medical Centre

Patient X is a 33-year old single man, who was first admitted to the psychiatric department due to major depression. He was treated with zoloft, recovered completely and was able to return to work.
The second hospitalization was due to a manic episode with psychotic symptoms. The patient was also diagnosed with multiple somatic complications, all liked to HIV infection. He was treated with Seroquel XR and referred to an HIV specialist.
We are currently looking into a treatment dilemma, because the patient is receiving Highly Active Antiretroviral Therapy (HAART) with protease

inhibitors that are not recommended together with most of the psychotropic drugs. The HIV specialist has banned Seroquel XR treatment.

We do not seem to have sufficient knowledge on the interactions of HAART treatment and antipsychotics. The patient is again in depressive phase and we have still not found suitable and effective treatment.

Pavel Toropov
Psychiatry Clinic, North Estonia Medical Centre

Dramatic effect of Aripiprazole on hyperactivity disorder
10 years old boy. First psychiatric consultation took place in 2008. Problems became actual in the 1 class. The main problems were connected with behaviour – inability to control the behaviour, impulsivity, verbal and physical aggression towards peers and parents, hedonic behaviour (video games, films). A lot of problems in interaction with teachers (insulting, manipulating, arguing). Learning skills were always excellent.
Family: patient, mother, father-in-law (patient thinks he is a biological father). Mother is emotional, but sensible woman; father-in-law highly educated, stone cold. Milieu is normal.
Patient was diagnosed with attention deficit and hyperactivity disorder (ICD 10; F90.0) Treatment with methylphenidate (Ritalin 10 mg x2) was initiated. Minimal to moderate effect on behaviour was marked (decrease of impulsivity, increase of self-control). Mother was very upset because of using central stimulants and decided not to use it any more. Patient lived many months without any specific medication.
18.05.2010 – 28.05.2010 first hospitalization because of conduct disorder. Diagnosis F90.0, many consultations with mother for treatment continuation using central stimulants. Agreed.
Step 1: Concerta 36 mg - without any significant effect. Problems at school and home.
Step 2: Riperidone was added to control the impulsivity 0,5 mg at night > 1 mg x 2 – without significant effect. Increase in body weight.
Step 3: Concerta 36 mg + Buspirone (Buspar 10 mg x3) – no effect.
01.09.2010 – parents decided to change the school. In a new school problems with behaviour became actual in 2 months.
03.01.2011 – 21.01.2011 – second hospitalization because of robust conduct disorder.
Tab. Aripiprazoli 7,5 mg (Abilify). Dramatic effect in a few days. No impulsivity, no aggression, normal behaviour at school and home. Teachers were amazed.

New problems for clinician: intensive enuresis, tic disorder became actual (dancing like movements), problems with learning skills, increase in body weight.
What to do?
Aripiprazle 7,5 mg > 3,75 mg
What is next?

Ere Vasli
Psychiatry Clinic, North Estonia Medical Centre

30 year old male patient presenting with depressed and irritable mood, anxiety, occasional paranoid delusional interpretation of neutral situations accompanied with hostile behaviour. According to medical history the first psychiatric admission was at the age of 12 (diagnosed with conduct disorder), later two admissions with substance overdose, once accompanied with brain concussion due to accident, once with suicide attempt. Patient had been convicted with car theft and spent 1,5 years in jail.

Patient was diagnosed with unstable personality disorder (different diagnostically depression with psychotic symptoms, bipolar disorder were considered). Intended drug treament of the patient was complicated with somatic contradictions and different, improbable side-effects.

For ambulatory care a drug treament programm with carbamazepin and risperidon combination and psychological support with weekly meetings with a cognitive behavioural therapist were fixed.

Flo Vilgats
Psychiatry Clinic, North Estonia Medical Centre

Case Report
A woman 65 years old hospitalized 4th time. Her symptoms began about 2 years ago, when she complained different pains in her body, sleep disturbancies, fear of different diseases. She felt tired all the time. In September 2009, she was at internal ward. No serious illness was detected.
April 2010 she was hospitalized at the psychiatrical ward, where she received the diagnosis of undifferentiated somatoform disorder.
Now she is at hospital again, and the she has almost the same complaints as 2 years ago. She has been treated with different antidepressants and antipsychotics but without effect.

Mairi Zopp
Psychiatry Clinic, North Estonia Medical Centre

In collaboration with Tallinn University of Technology our group intends to examine the effect of electroconvulsive therapy on brain neurophysiology in depressive patients. We are interested to find out if they are related to stimulus parameters (pulse width, frequency, duration) and electrode placement (bilateral vs right-unilateral) selection. We also intend to examine the effect of ECT on cognitive functions, changes in gene-expression. Our aim is also to find out if some of these changes persist over for longer period (6 months).

Kairit Zovo
Department of Gene Technology, Tallinn University of Technology

Aggregation of amyloid-b (Ab) peptides is causatively linked to Alzheimer's disease (AD); thus, suppression of this process by small molecule inhibitors is a widely accepted therapeutic and preventive strategy for AD. Screening of the inhibitors of Ab aggregation deserves much attention; however, despite intensive efforts, there are only a few high-throughput screening methods available, all of them having drawbacks related to the application of external fluorescent probes or artificial Ab derivatives. We have developed a label-free MALDI MS-based screening test for inhibitors of Ab42 fibrillization that exhibits high sensitivity, speed, and automation possibilities suitable for high-throughput screening. The test was evaluated by transmission electron microscopy and compared with a fluorimetric thioflavin-based assay, where interference of a number of tested compounds with thioflavin T binding and/or fluorescence caused false-positive results. The MALDI MS-based method can significantly speed up in vitro screening of compound libraries for inhibitors of Ab42 fibrillization.

ECNP

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