Working mechanisms of antidepressants

Dr. H.G. (Henk) Ruhé MD PhD
Program for Mood and Anxiety Disorders
University Medical Center Groningen
H.G.Ruhe@UMCG.NL

Conflicts of interest:
-Speaking fees Astra Zeneca & Lundbeck
-IIT support Lundbeck

Major Depressive *Episode*

Introduction

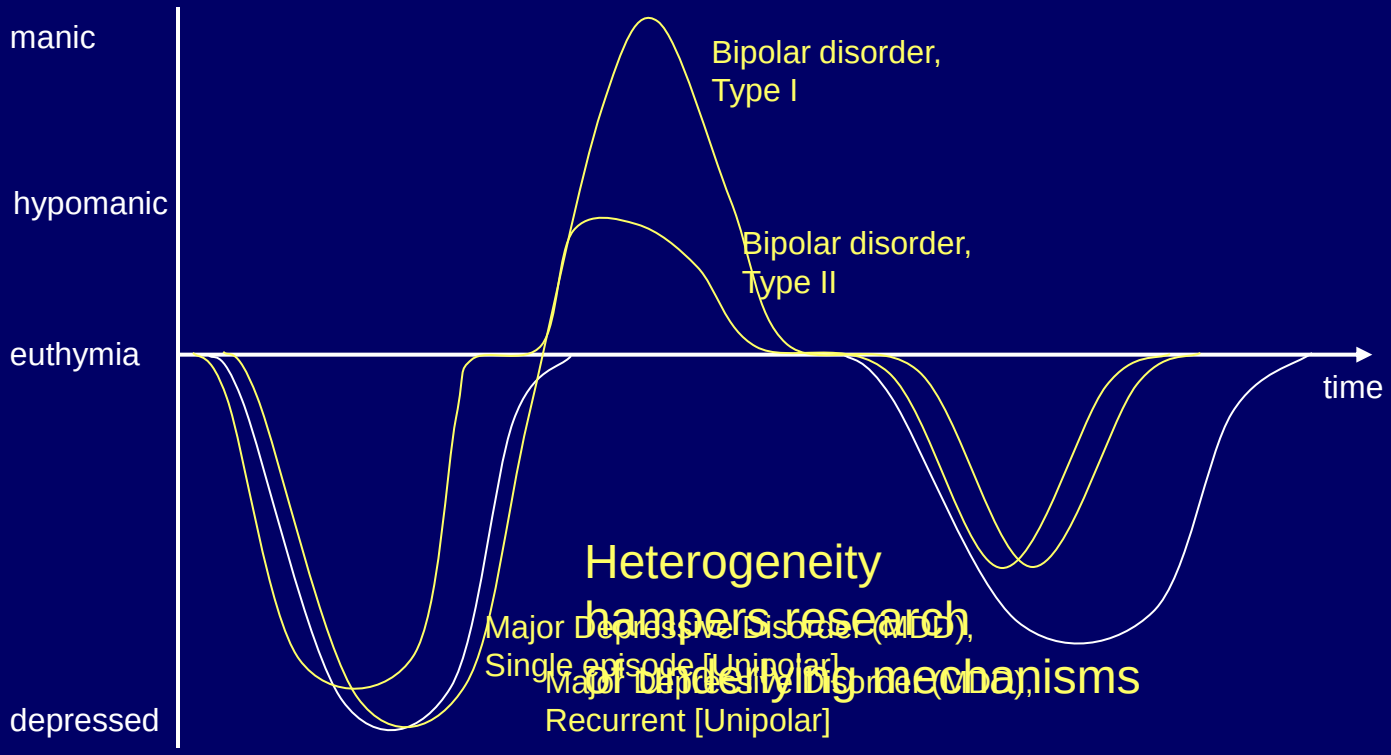
Monoamine hypothesis
- chemical
- time lag
- psychol.

Beyond monoamines

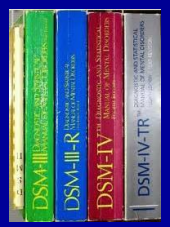
Networks

Discussion

Different time courses with/without mania determine the type of affective disorder:



DSM-IV TR, 2000



Affective Disorders 'Depression'

- Unipolar
- Bipolar

High-income countries	1	Unipolar depressive disorders	9.8
	2	Ischaemic heart disease	5.9
	3	Alzheimer and other dementias	5.8
	4	Alcohol use disorders	4.7
	5	Diabetes mellitus	4.5
	6	Cerebrovascular disease	4.5
	7	Hearing loss, adult onset	4.1
	8	Trachea, bronchus, lung cancers	3.0
	9	Osteoarthritis	2.9
	10	COPD	2.5

- high costs

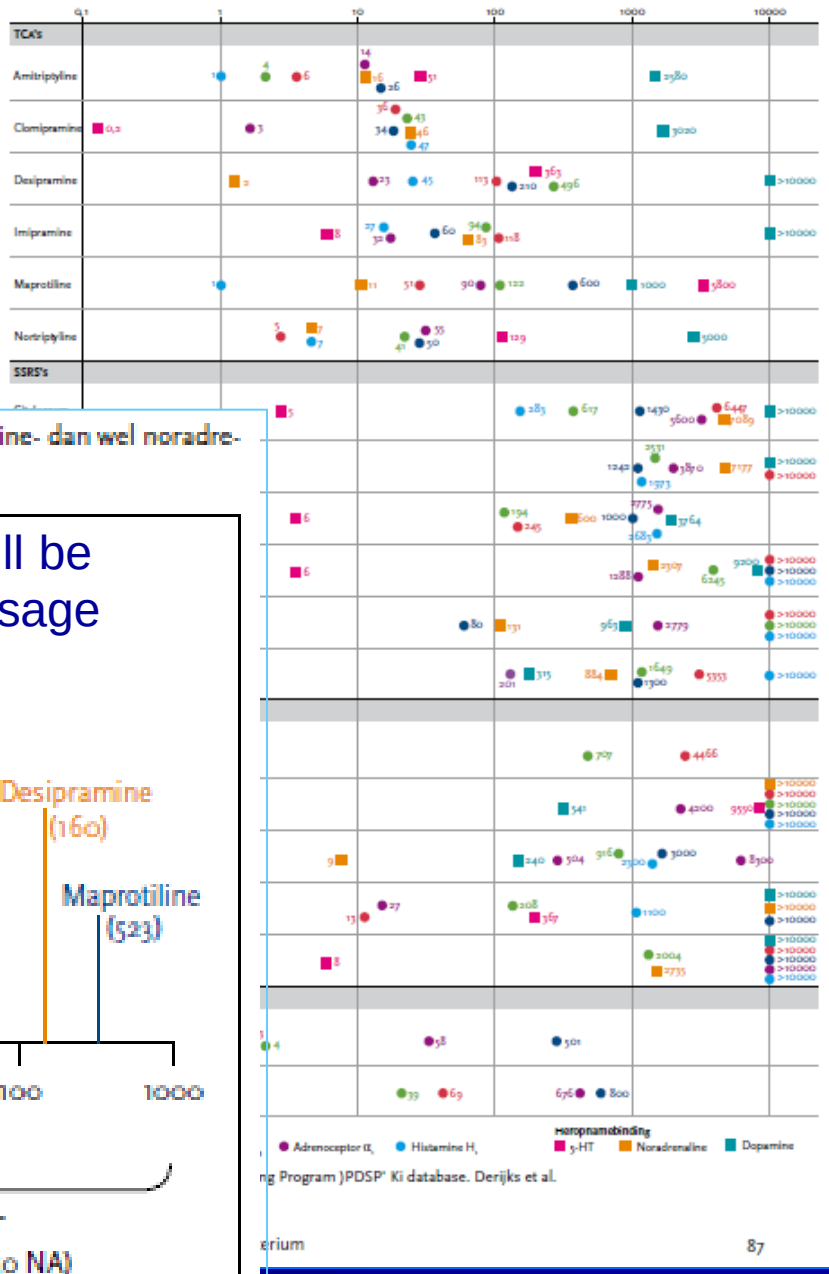
- high costs
- 10% of work disability caused by MDD
- #1 costs/DALYs in 2030

Wittchen et al., 2011

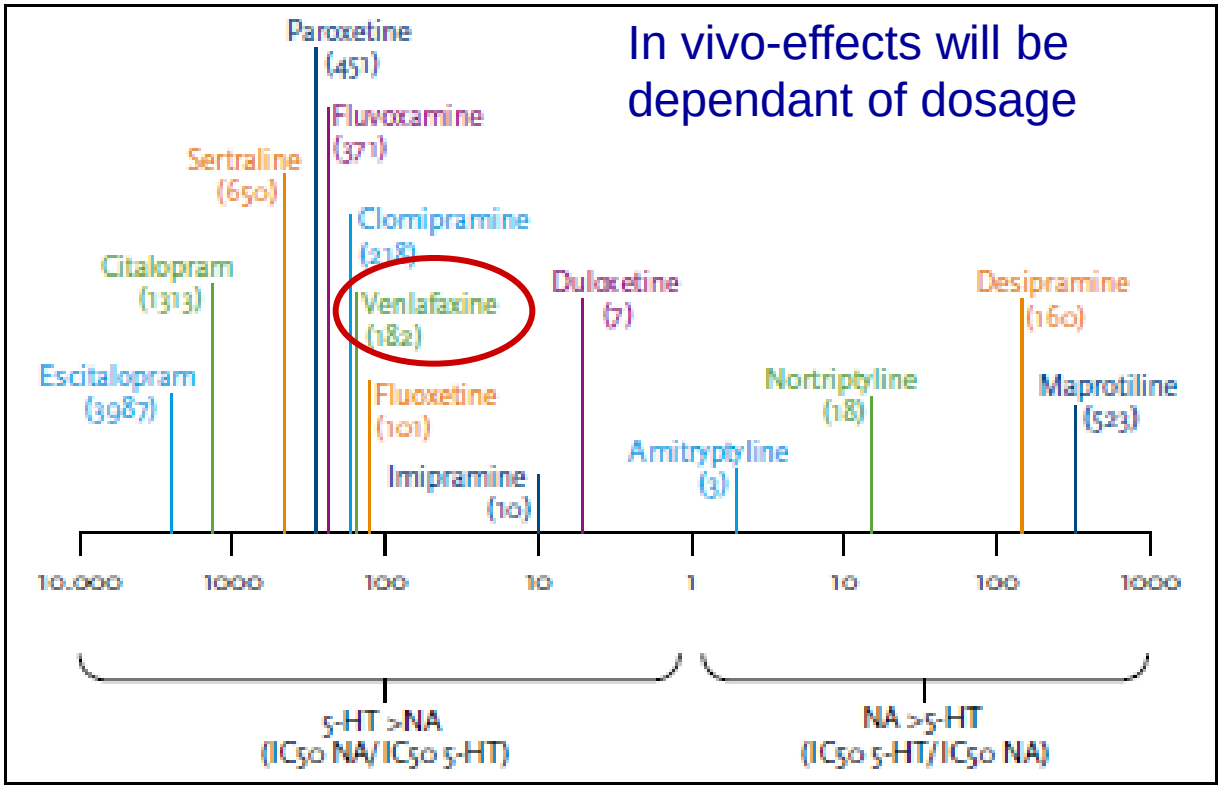
Treatment of Antidepressa

- SSRI

Affinity of ADs for transporters and receptors



Figuur 2. Overzicht van de relatieve selectiviteit van SSRI's en TCA's voor de serotonine- dan wel noradrenalinetransporter.



In vivo-effects will be dependant of dosage

Bron: The Psychoactive Drug Screening Program (PDSP); http://pdsp.med.unc.edu

Keuzecriteria Antidepressiva. 2010;83-101
Keuzecriteria Antidepressiva. 2010;11-27

To discuss today

- ✓ Introduction
- Monoamine hypothesis
- Beyond monoamines
- Brain function and antidepressants
- The future

Monoamine hypothesis

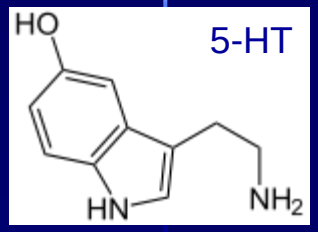
- Discovery of antidepressants by serendipity
  - ~1950-ties Iproniazide; Imipramine
  - Reserpine
- Mechanisms??
  - Iproniazide -> MAO-I
  - Imipramine -> blockade of SERT/NET
  - Reserpine -> ↓neurotransmitter in vesicles

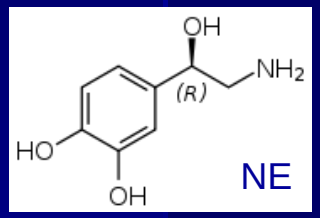
➢ **Monoamine hypothesis**

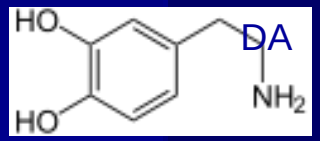
MDD is *caused* by loss of 5-HT, NE (DA)

Crane. Am J Psychiatry 1956;112:494-501
Kuhn R. Am J Psychiatry 1958;115:459-464

Monoamine-hypothesis: 'challenging the system'







- Experimental ↓5-HT
  - acute tryptophan-depletion (ATD)
  - para-chlorophenylalanine (PCPA)
- Experimental ↓NE, DA
  - acute phenylalanine/tyrosine depletion (APTD)
  - α-methyl-para-thyrosine (AMPT)
- vs placebo-depletion (double blind)
- Cross-over / between groups design
- 1-3 days
- >90 studies: stratified meta-analysis

Ruhe e.a. Mol Psychiatry 2007;12:331-359

Monoamines: ATD, 5-HT & mood

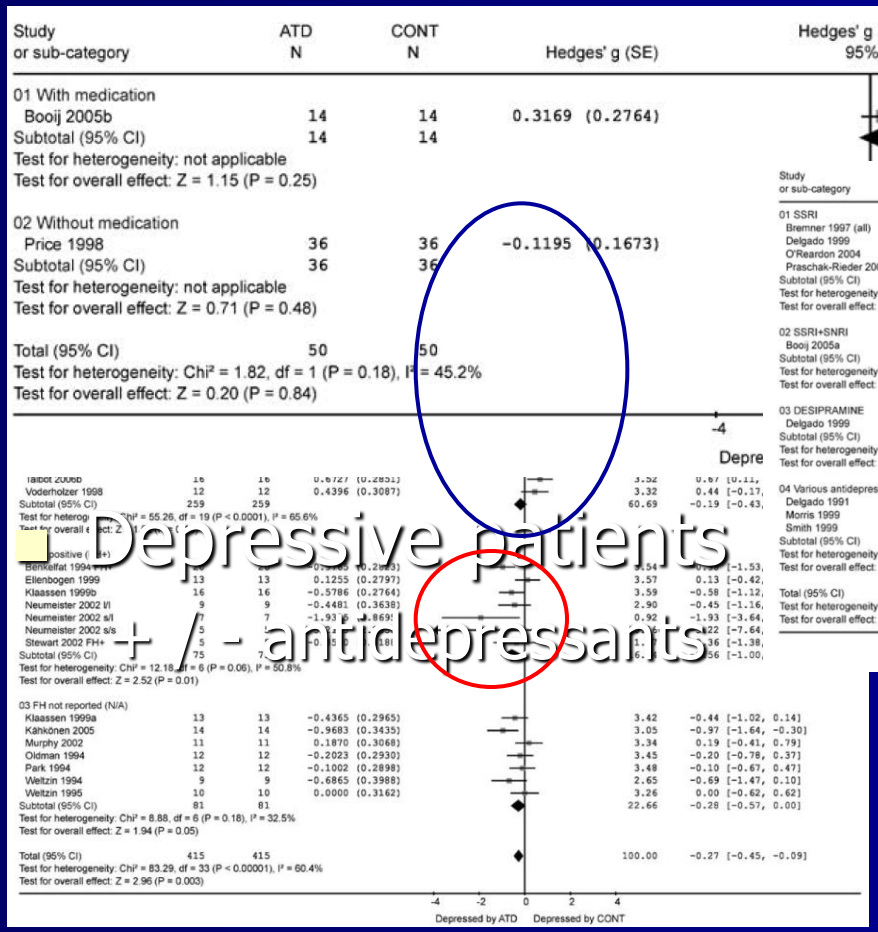
Molecular Psychiatry (2007), 1–29
© 2007 Nature Publishing Group All rights reserved 1359-4184/07 $30.00
www.nature.com/mp

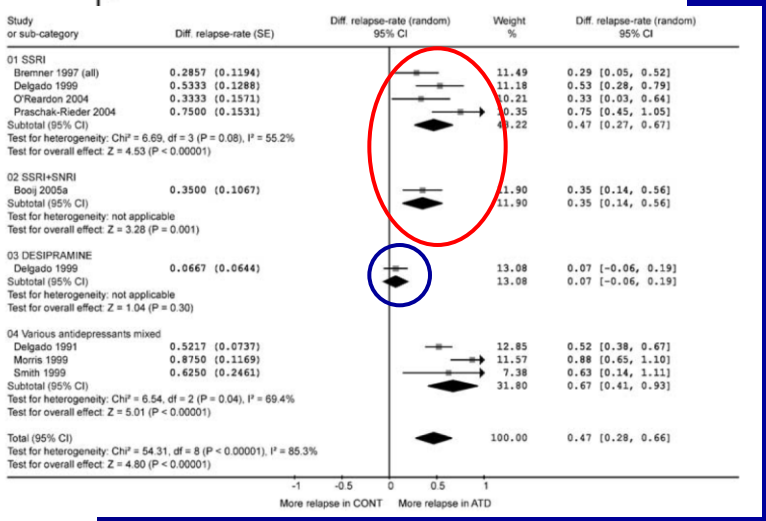
FEATURE REVIEW

Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies

HG Ruhé, NS Mason and AH Schene

Program for Mood Disorders, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands





Ruhe e.a. Mol Psychiatry 2007;12:331-359

Monoamines: indirectly associated MDD

Introduction

Monoamine hypothesis
- chemical
- time lag
- psychol.

Beyond monoamines

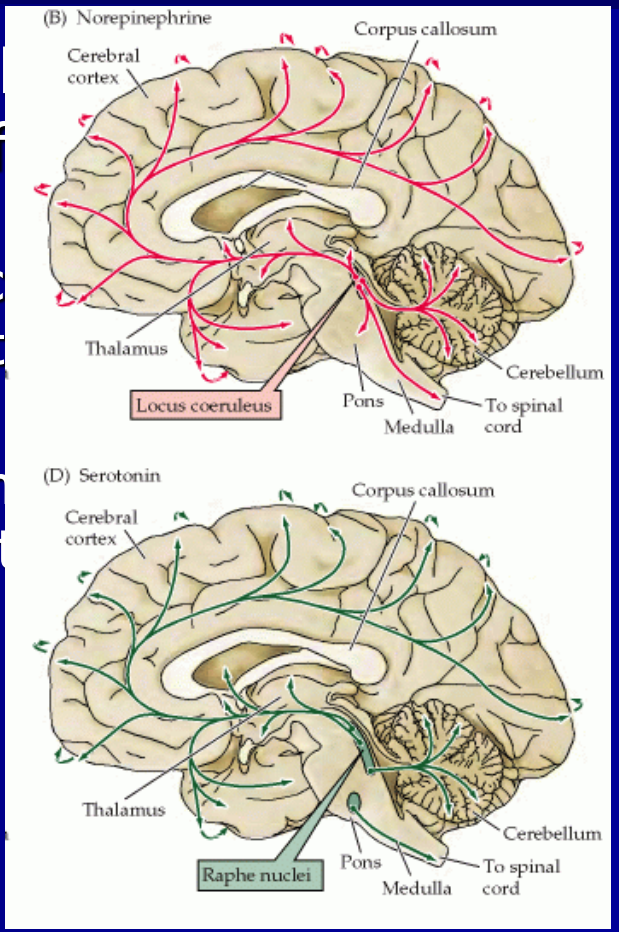
Networks

Discussion

- No direct effects of 5-HT, N
- Unless already 'vulnerable' f
  - Family affected
  - Previous MDD (incl. recurrenc
  - Use of specific antidepressant
- Discrete effects on:
  - Cognition: ↓↓ 'learning' & mer
  - ↑↑ Attention & executive funct

  ~ effects seen in MDD

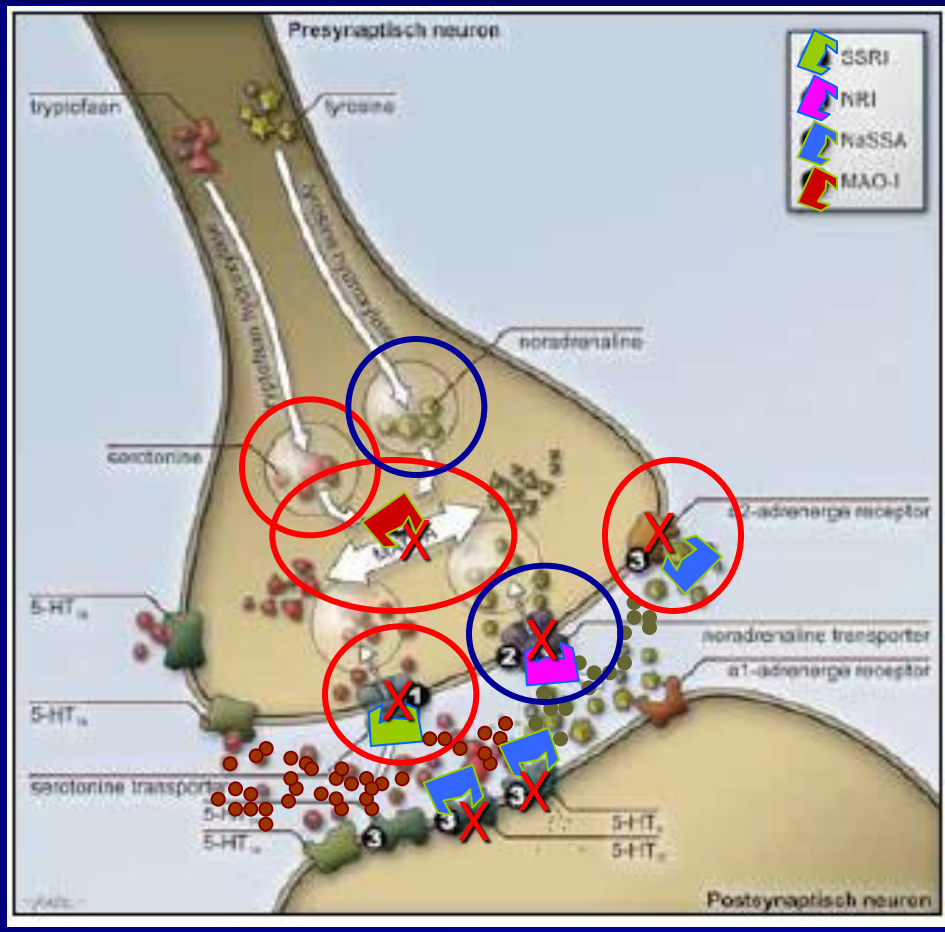
Final common pathway ??
5-HT -> inhibition



Purves e.a. Neuroscience 2nd ed. 2001

Antidepressants:
Reuptake inhibitors [SSRI/SNRI/TCA]

- Monoamine-deficiency
- Synapse 5-HT/NE
- Blocking serotonin/NE transporters (SERT & NET)
- Within minutes after 1st dose
- NaSSA
- MAO-inhibitors

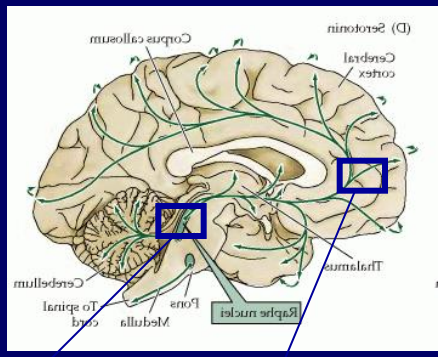


Homberg e.a. Keuzecriteria Antidepressiva. 2010;11-27

Why does it take so long before clinical effects appear??

- De-sensitization of 5-HT_{1A} / 5-HT_{1B} autoreceptors
- 2^{nd} – 4^{th} messenger effects
- Effects occur, but we don't notice it earlier

Desensitization
5-HT$_{1A/1B}$ (α_2) autoreceptors



- Introduction
- Monoamine hypothesis
  - chemical
  - time lag
  - psychol.
- Beyond monoamines
- Networks
- Discussion

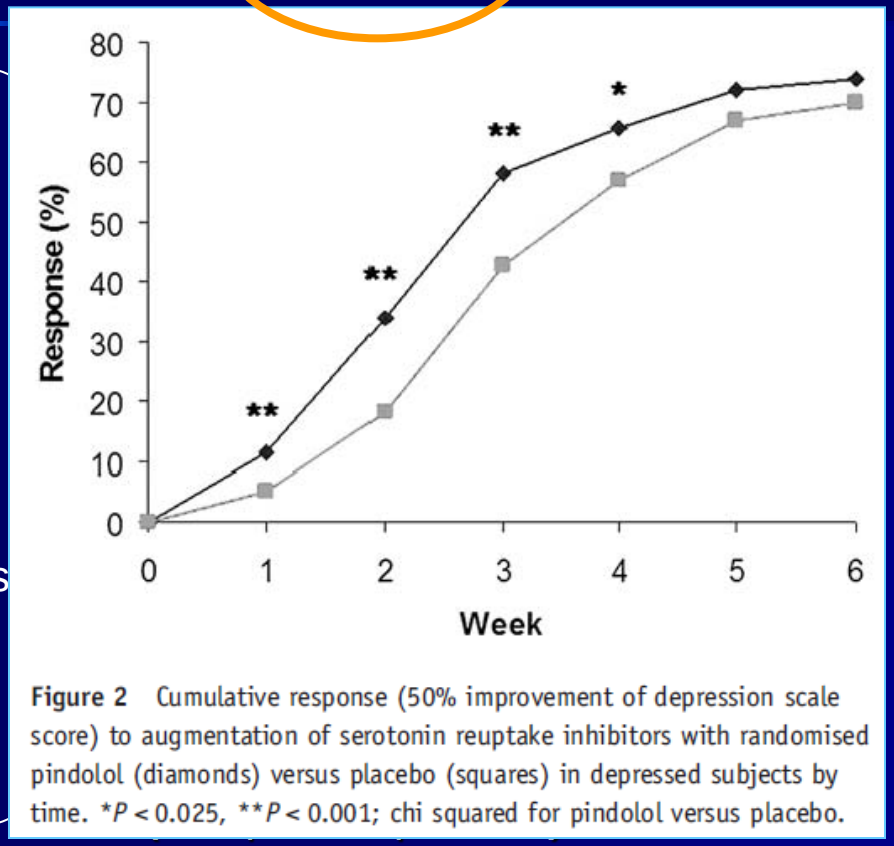
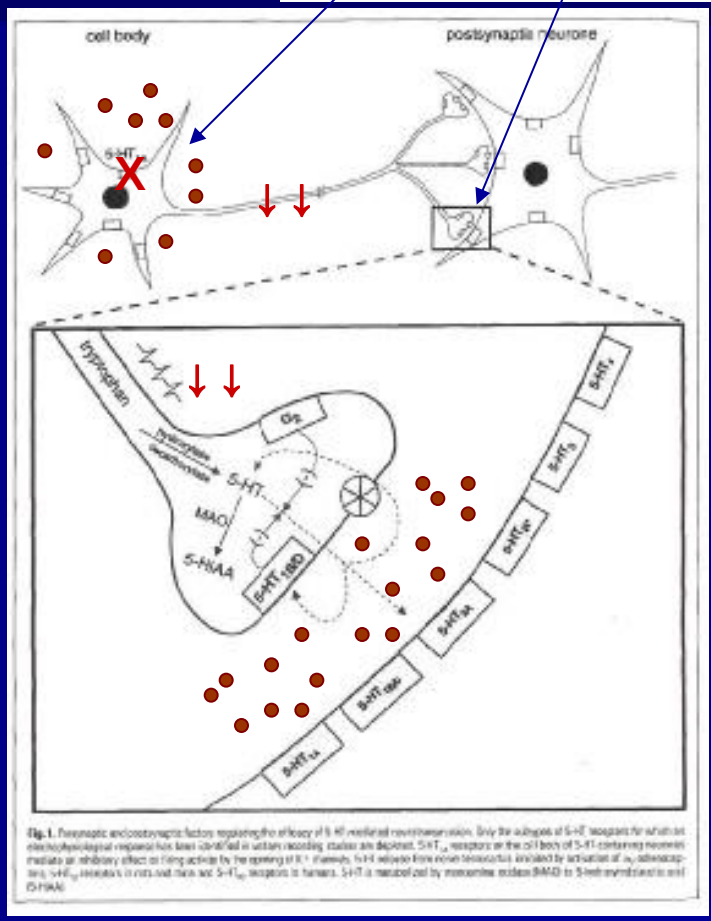


Figure 2 Cumulative response (50% improvement of depression scale score) to augmentation of serotonin reuptake inhibitors with randomised pindolol (diamonds) versus placebo (squares) in depressed subjects by time. *$P < 0.025$, **$P < 0.001$; chi squared for pindolol versus placebo.



5-HT$_{1A}$ antagonist: pindolol
- Hastens response in SSRIs

Blier e.a. TiPS 1994;15:220-6
Homberg e.a. Keuzecriteria Antidepressiva. 2010
Bel e.a. Synapse 1993;15:243-5
Whale e.a. J Psychopharmacol 2010;24:513-20

2nd – 4th messengers

Introduction

Monoamine hypothesis
- chemical
- time lag
- psychol.

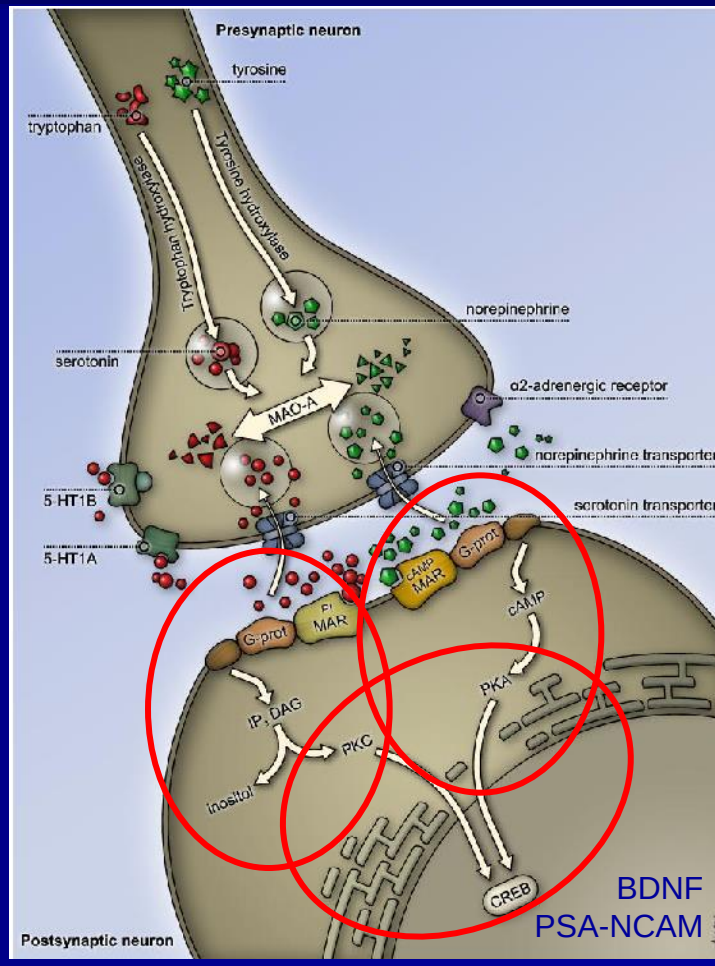
Beyond monoamines

Networks

Discussion

Post-synaptic G-protein receptors

- Phosphatidyl-inositol (PI)-coupled
  - phospholipase C
    - Inositol triphosphate (IP3) / diacylglycerol (DAG)
    - protein kinase C (PKC)
- cAMP-coupled
  - cAMP
  - protein kinase A (PKA)
- PKC / PKA
  - cAMP responsive element binding (CREB)
- Regulation gene expression
  - E.g. BDNF, polysialated neural cell adhesion molecule (PSA-NCAM)
- NB: effects of AD via ↑ CREB differ per region in the brain



Belmaker e.a. NEJM 2008;358:55-68
Homberg e.a. Keuzecriteria Antidepressiva. 2010;11-27

Effects do occur early… but we don't notice

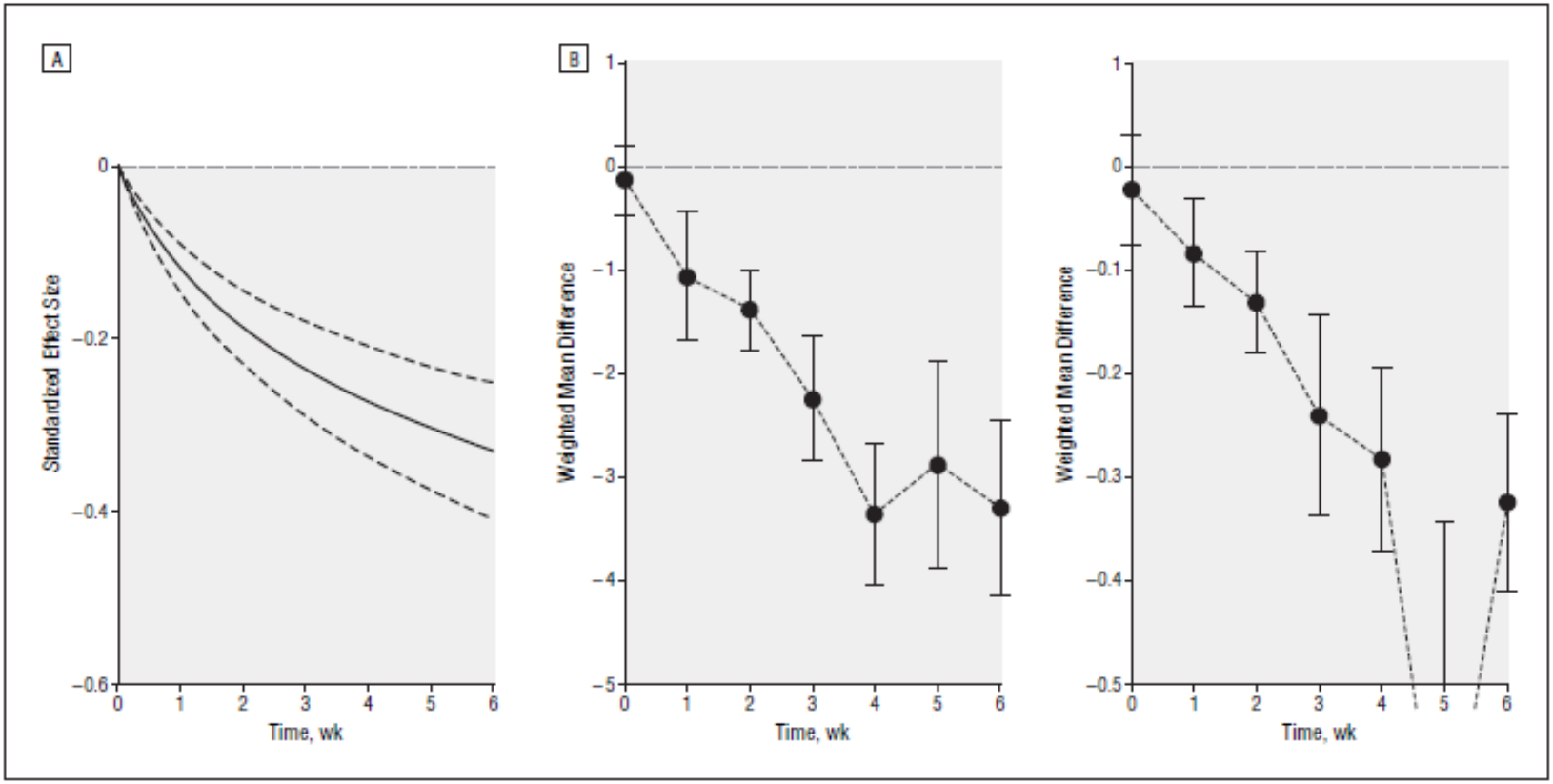


Figure 2. Differences in depression symptom rating scale scores across time between groups treated with selective serotonin reuptake inhibitors and placebo. A, Best-fit model (logarithmically increasing treatment response) for the difference in standardized effect size between groups (placebo: n=2254 and selective serotonin reuptake inhibitor: n=3618) Dotted lines represent 95% confidence intervals. B, Weighted mean difference in scores using the Hamilton Depression Rating Scale (left) (n=1893-3433) and the Montgomery-Asberg Depression Rating Scale (right) (n=133-3159). Error bars represent 95% confidence intervals.

Taylor e.a. Arch Gen Psychiatry 2006;63:1217-23

Effects do occur early… but we don't notice

2nd:

- Negative biases in emotional processing are a hallmark of depressive illness
- These biases may be targeted early in treatment
  - before changes in mood occur
  - play a key role in later improvement of symptoms

Harmer e.a. Br J Psychiatry 2009;195:102-8

Early effects of antidepressant drug administration are seen in depression

Introduction

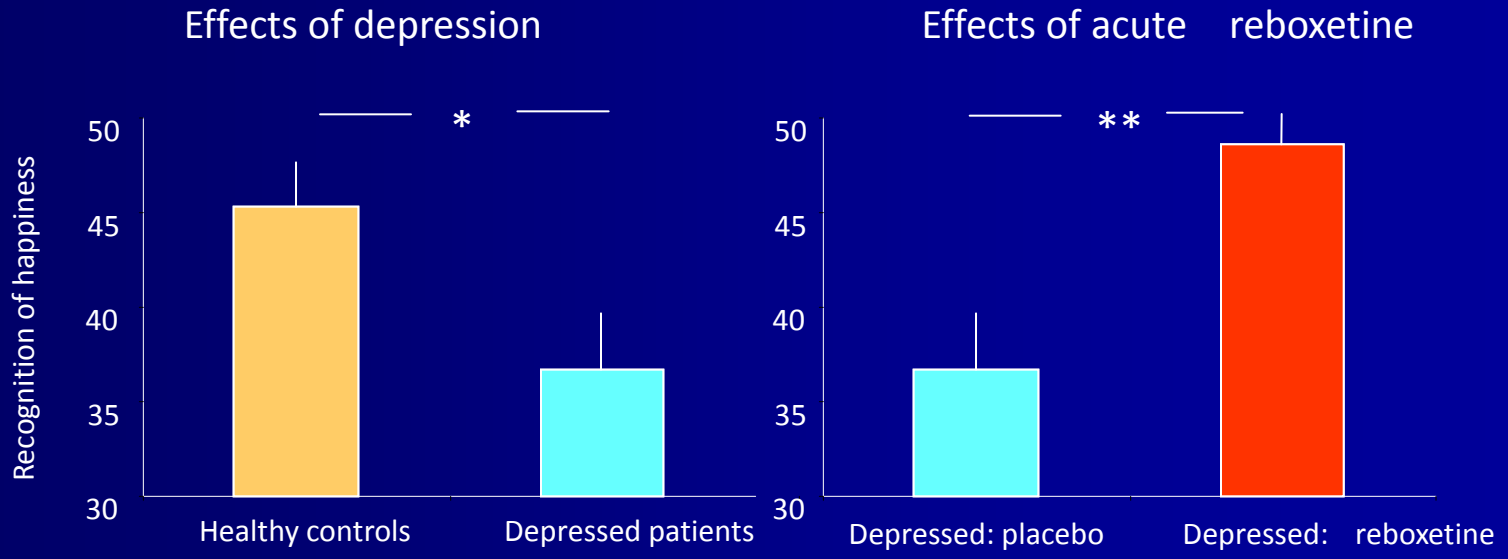
Monoamine hypothesis
- chemical
- time lag
- psychol.

Beyond monoamines

Networks

Discussion

- MDD: n= 33; controls: 31
- Emotional processing: emotional biases facial expression recognition task (FERT), emotional categorization & memory
- Face recognition 3 hours after 1st dose



Harmer e.a. Am J Psychiatry 2009;166:1178-84

Mechanisms of action of antidepressants

Introduction

Monoamine hypothesis
- chemical
- time lag
- psychol.

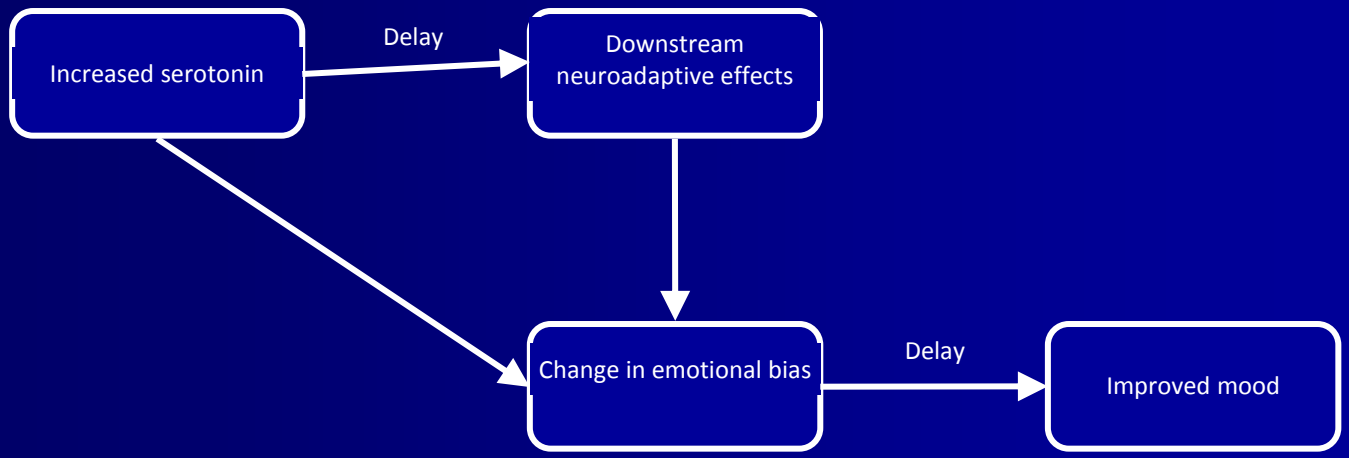
Beyond monoamines

Networks

Discussion

- Model

Cognitive Neuropsychological Model



Harmer e.a. Br J Psychiatry 2009;195:102-8
Harmer e.a. Am J Psychiatry 2009;166:1178-84

Early changes in bias are predictive of later changes in symptoms

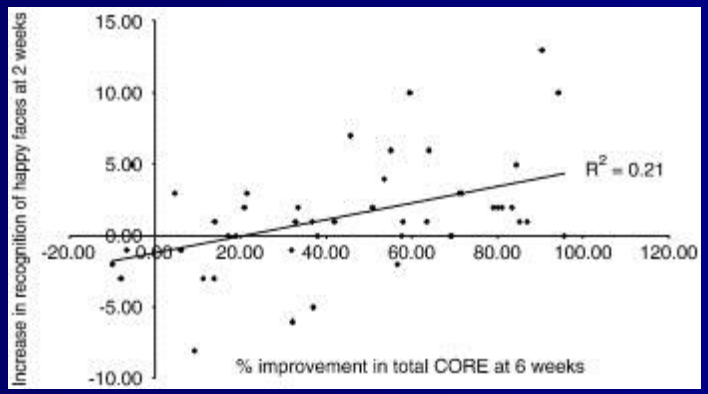
Introduction

Monoamine hypothesis
- chemical
- time lag
- psychol.

Beyond monoamines

Networks

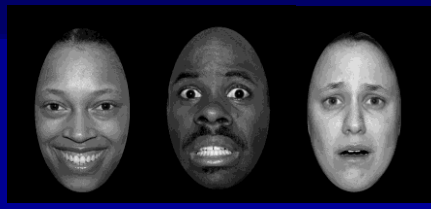
Discussion



- Improvement in happy recognition following two weeks antidepressant treatment predicted clinical outcome at week 6

Tranter e.a. J Affect Disord 2009;118:87-93

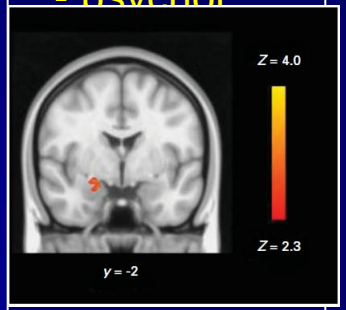
Neuroimaging: Changes in bias: amygdala response to fear/happy stimuli (UD)



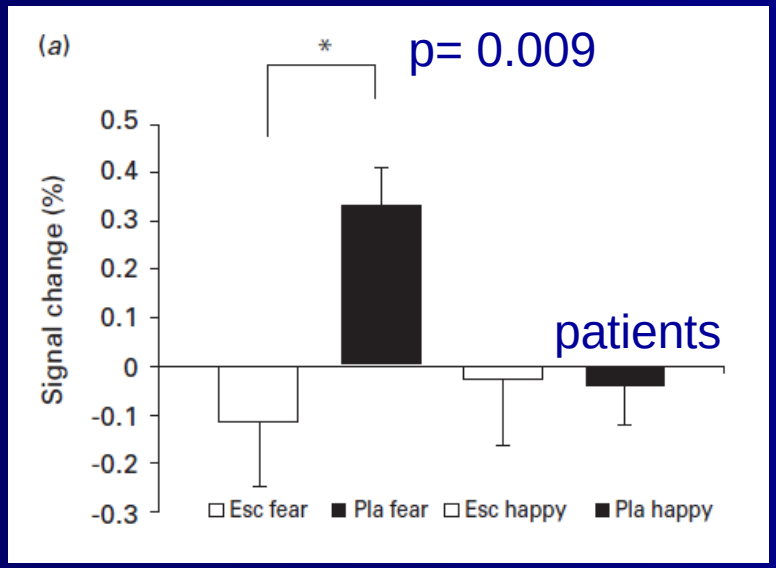
- MDD: n= 42; controls: 17
- MDD Randomized escitalopram / plac.
- fMRI covert faces after 1 wk!!

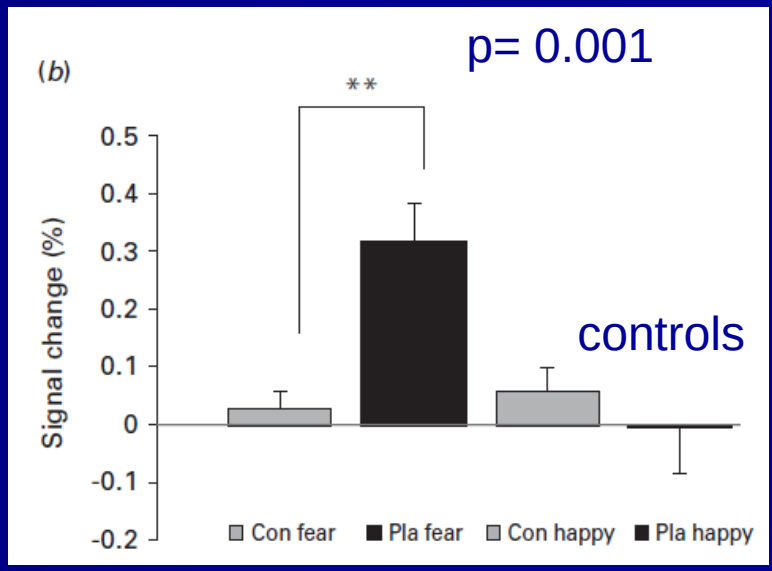
Introduction

Monoamine hypothesis
- chemical
- time lag
- psychol



Discussion





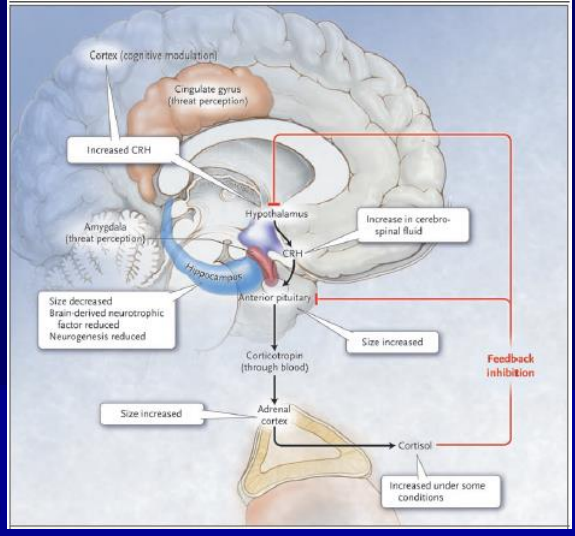
Godlewska e.a. Psychol Med 2012;E-pub 25th April

Beyond monoamines (1)

- Circadian rhythm changes
  - Sleep problems
  - Increased REM-sleep in MDD
  - Diurnal rhytm cortisol/melatonin
- Treatments
  - TCAs, MAO-I ↑REM-latency and ↓total REM
  - Synchronisation of biological clock
    - Structure and regularity
    - Sleep deprivation
    - Bright light
  - Agomelatin
    - Agonism melatonin $MT_{1/2}$ receptor
    - Antagonism 5-HT_{2C}

Homberg e.a. Keuzecriteria Antidepressiva. 2010;11-27

Beyond monoamines (2)



- HPA-axis changes
  - Increased levels cortisol, CRH in MDD
  - Abnormal Dex-CRH test in 50% of MDD
  - ↓sensitivity of glucocorticoid receptors
  - Non-specific
  - Especially in severe & psychotic MDD
- Treatments
  - SSRIs/TCAs
    - ↑serotonergic neurotransmission
    - Limbic projections to (hypo-)thalamus
    - Increase glucocorticoid sensitivity
- mifepristone [RU-486], ketoconazole, metyrapone, DHEA
  - Potential interest, but not in psychotic MDD

Homberg e.a. Keuzecriteria Antidepressiva. 2010;11-27
Belmaker e.a. NEJM 2008;358:55-68
Pariante. Ann N Y Acad Sci 2009;1179:144-52
Gallagher e.a. Cochrane Database Syst Rev. 2008;1:CD005168

Chemical hypothesis versus network hypothesis

Introduction

Monoamine hypothesis
- chemical
- time lag
- psychol.

Beyond monoamines

Networks

Discussion

OPINION

Is mood chemistry?

Eero Castrén

Abstract | The chemical hypothesis of depression suggests that mood disorders are caused by a chemical imbalance in the brain, which can be corrected by antidepressant drugs. However, recent evidence indicates that problems in information processing within neural networks, rather than changes in chemical balance, might underlie depression, and that antidepressant drugs induce plastic changes in neuronal connectivity, which gradually lead to improvements in neuronal information processing and recovery of mood.

PERSPECTIVES

NATURE REVIEWS | NEUROSCIENCE VOLUME 6 | MARCH 2005 | 241

BDNF

Box 1 | **Activity-dependent refinement of neural networks**

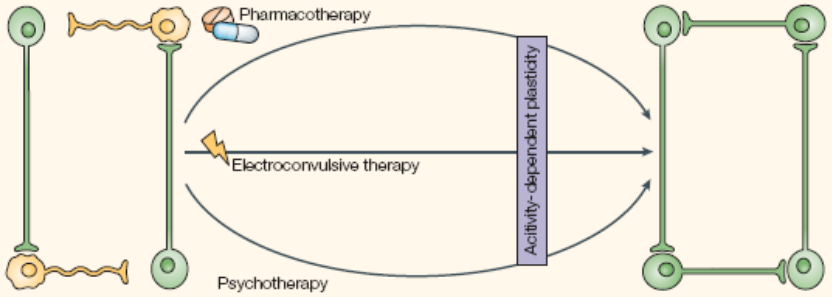
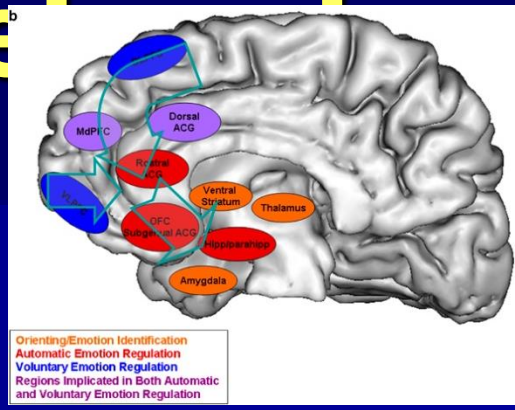


Figure 4 | **A combinatorial approach for treating depression based on the network hypothesis.**

Castrén. Nat Rev Neurosci 2005;6:241-246

The fronto-limbic ne

- Introduction
- Monoamine hypothesis
  - chemical
  - time lag
  - psychol.
- Beyond monoamines
- Networks
- Discussion



MDD: hyperactivation

Ventral system

negative attentional bias

Amygdala
Insula

Visual cortex

VLPFC
OFC
Ventral ACG

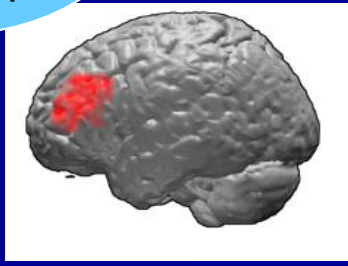
Thalamus
Ventral Striatum
Brainstem nuclei

MDD: hypoactivation

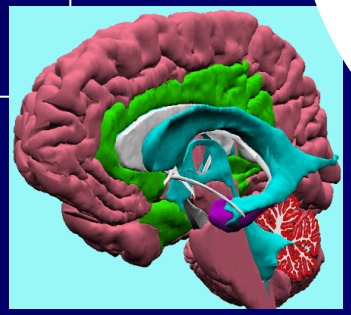
regulation

Dorsal PF system

DLPFC
DMPFC
Dorsal ACG
Hippocampus

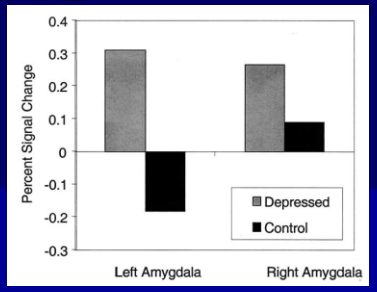


mood



Phillips et al. Biol Psychiatry 2003;54:515-28
Phillips et al. Mol Psychiatry 2008;13;833-58

Previous phMRI antidepressant treatment studies (emotional

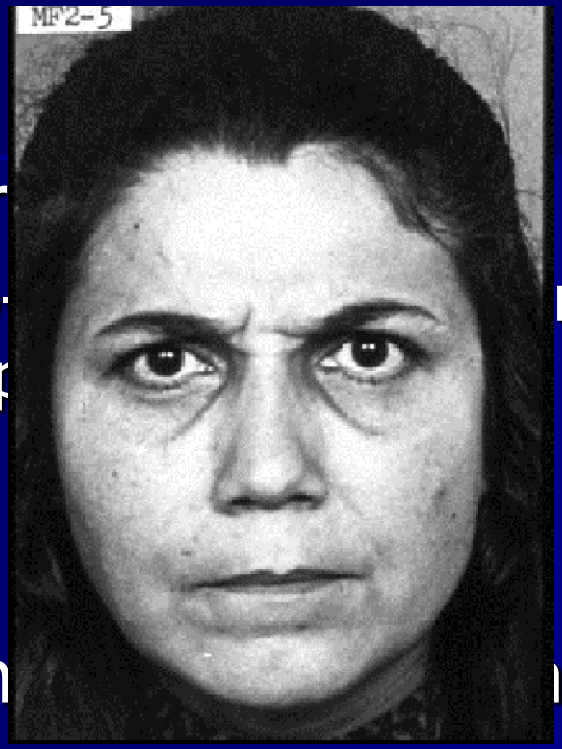


- Sheline: Faces, SER, n= 11, 8 wks
  - Amygdala (L+R) hyperactivation ↓↓ to level HC
- Davidson: IAPS, VLX, n= 12, 8 wks
  - ACG (L) hypoactivation ↑↑ (≥ level HC)
- Fu: Faces, FLX, n= 19, 8 wks
  - Limbic, subcortical ↓↓
  - Neocortical areas ↑↑
- Robertson: IAPS, BUP, n= 10, 8 wks
  - OFC (R), InfPFC (R), FG (R) en Amyg (L) ↓↓
  - InfPFC (L), FG(L) ↑↑

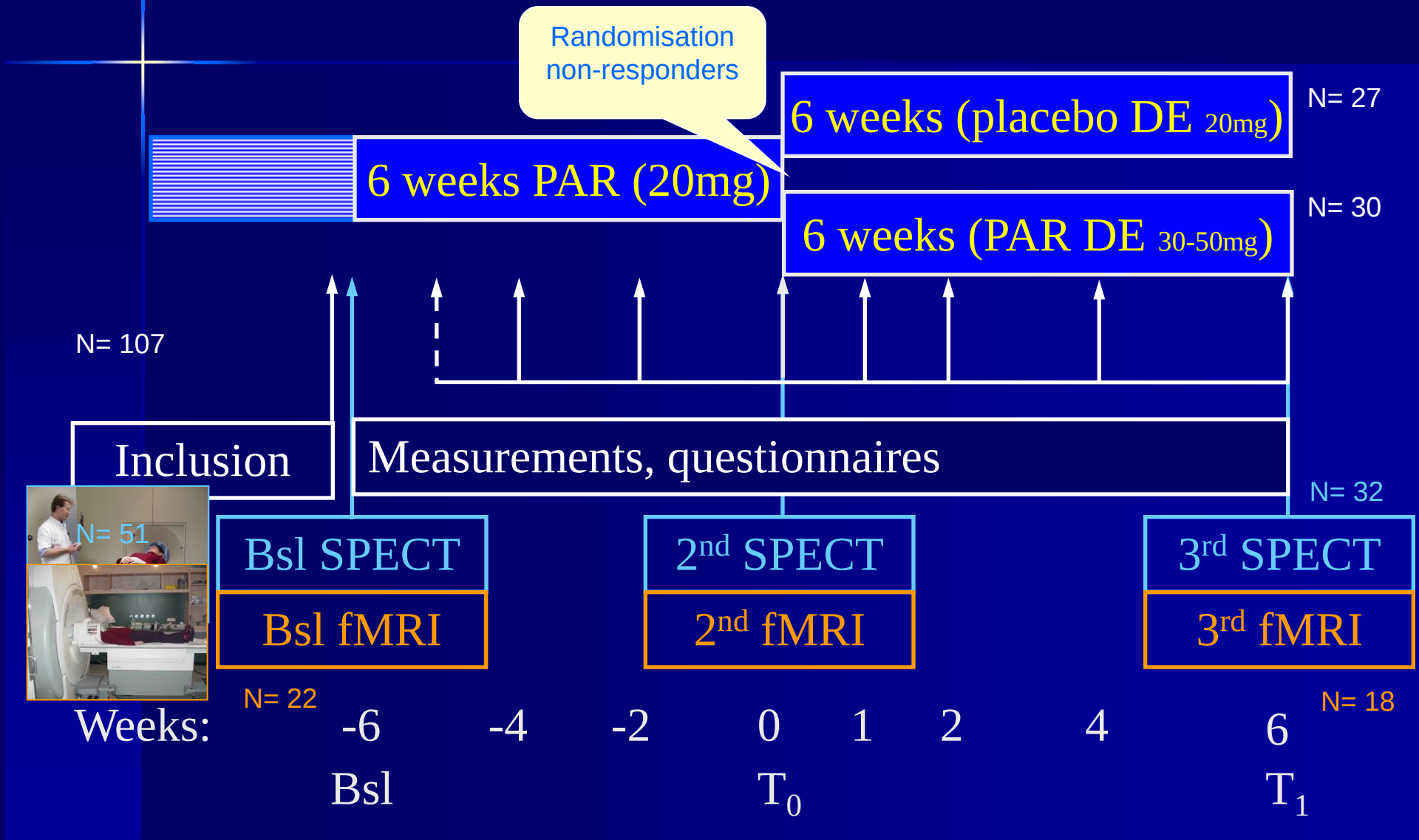
Sheline et al. Biol Psychiatry 2001; 50:651-8
Davidson et al. Am J Psychiatry 2003;160:64-75
Fu et al. Arch Gen Psychiatry 2004;61:677-89
Robertson et al. J Clin Psychiatry 2007;68:261-7

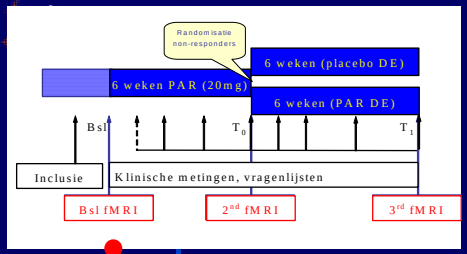
Objective

- Summar
  - Fronto- nges after use of antidep
- Function nces paradigm
  - Activation of the Amygdala ?
    - Pre-Tx: Increased activation depressed vs controls
    - Tx: Decrease in hyperactivation after treatment



DELPHI: Dose-Escalation Legitimate? PHarmacology and Imaging





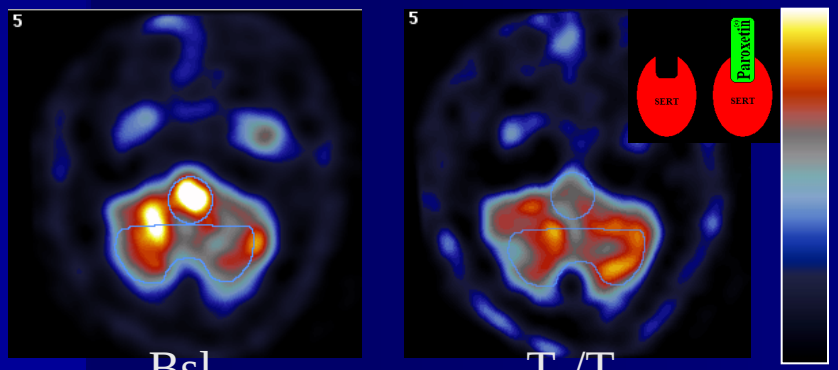
In- & exclusion criteria

- Inclusion
  - SCID MDD positive
  - HDRS > 18
  - Age 25-55 yrs
  - SPECT/fMRI-study: Drug-free >4 weeks
- Exclusion
  - Bipolar/psychotic disorder
  - Primary anxiety disorders
- Follow-up (n= 18):
  - Week 6: 5 responders, 13 NR (28%)
  - Week 12: 11 responders, 6 NR (65%)

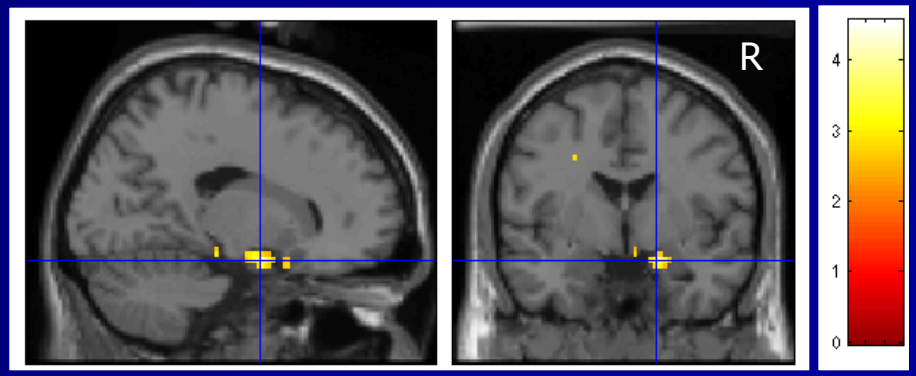
Ruhe et al. J Clin Psychiatry 2012;73:451-9

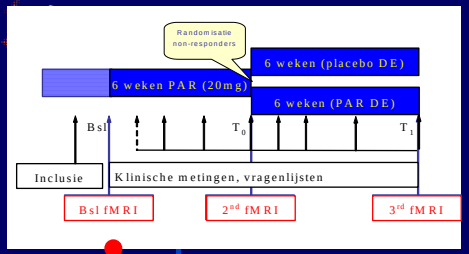
Imaging

- SPECT
  - Strichman 12 detector brain dedicated Neurofocus 810
  - 230 ±18 min after 100MBq [^{123}I]β-CIT
  - Reference: cerebelllum
  - $BP_{ND} = (Act_{RoI} - Act_{CER})/Act_{CER}$
  - $Occ = (BP_{BsI} - PB_{T0/T1})/BP_{BsI}$
- sMRI / fMRI
  - Philips Intera 3T
  - Event-related Faces (2500ms)
  - Sex-judgements
  - Angry/Fear vs scrambled
  - 250 EPIs BOLD
  - SPM5
  - RoI: amygdala



Bsl T_0/T_1





Functional MRI Patients vs. controls

Introduction

Monoamine hypothesis
- chemical
- time lag
- psychol.

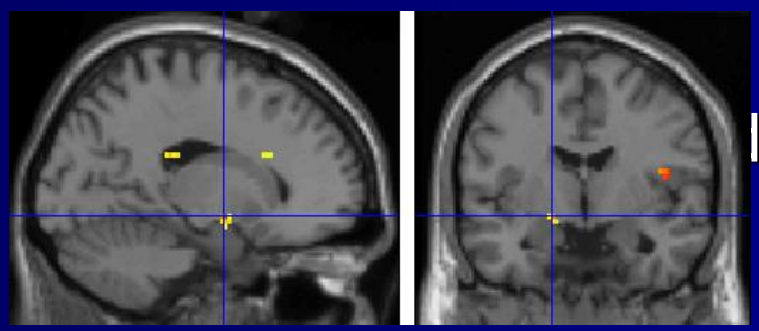
Beyond monoamines

Networks

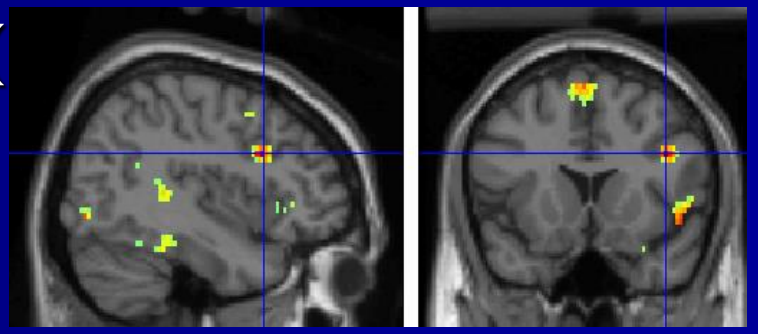
Discussion

- 43.3 ±7.9 yrs
- 14/22 male (64%)
- $HDRS_{17}$ 23.1 ±3.6
- Pre-Tx Patients > Controls
  - ↑↑ Depression and anxiety

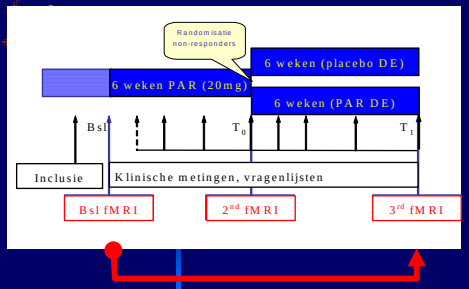
Pts > Cont. (



) Cont. > Pts

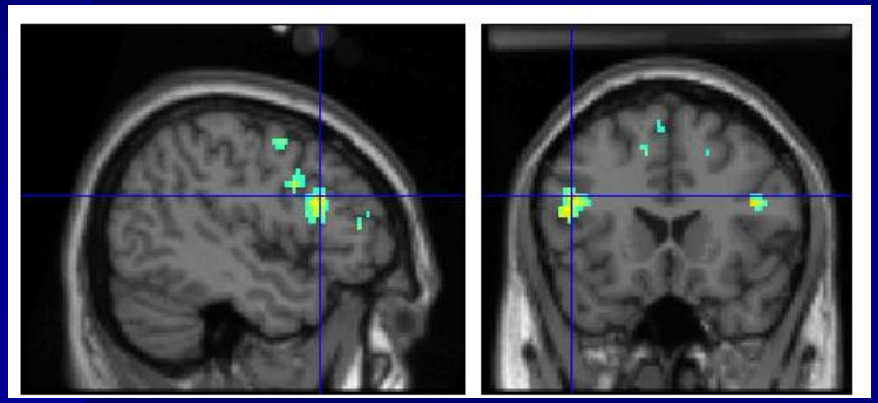


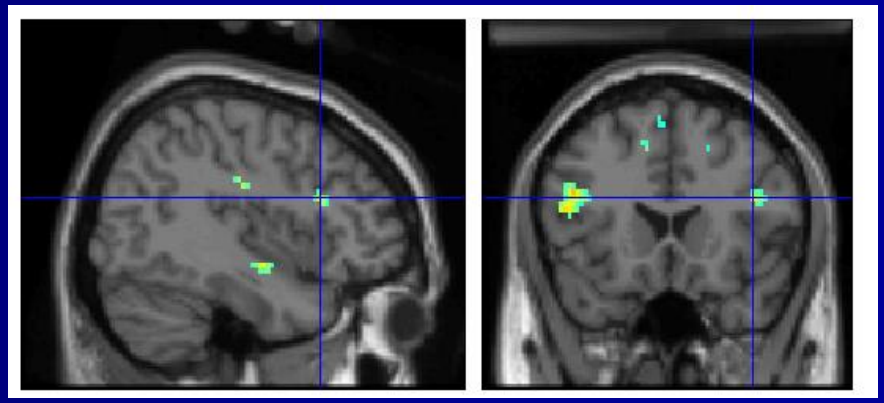
Ruhe et al. J Clin Psychiatry 2012;73:451-9



Functional MRI
Bsl -> Endpoint

- 12 weeks treatment:
  - Amygdala: no overall changes
  - But: ↑↑ activitions: DLPFC (L+R)





= Effects of antidepressants

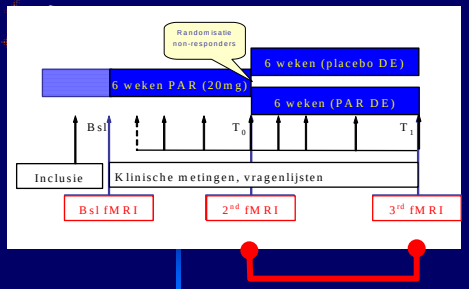
Ruhe et al. J Clin Psychiatry 2012;73:451-9

Previous studies of emotional stimuli and antidepressants (2)

- Sheline: Faces, SER, n= 11, 8 ws
  - Response: 10/11 (91%)
- Davidson: IAPS, VLX, n= 12, 8 wks
  - Response: 12/12 (100%, exclusion NR)
- Fu: Faces, FLX, n= 19, 8 wks
  - Response: 13/19 (68%)
- Robertson: IAPS, BUP, n= 10, 8 wks
  - Response: 6/8 (75%)

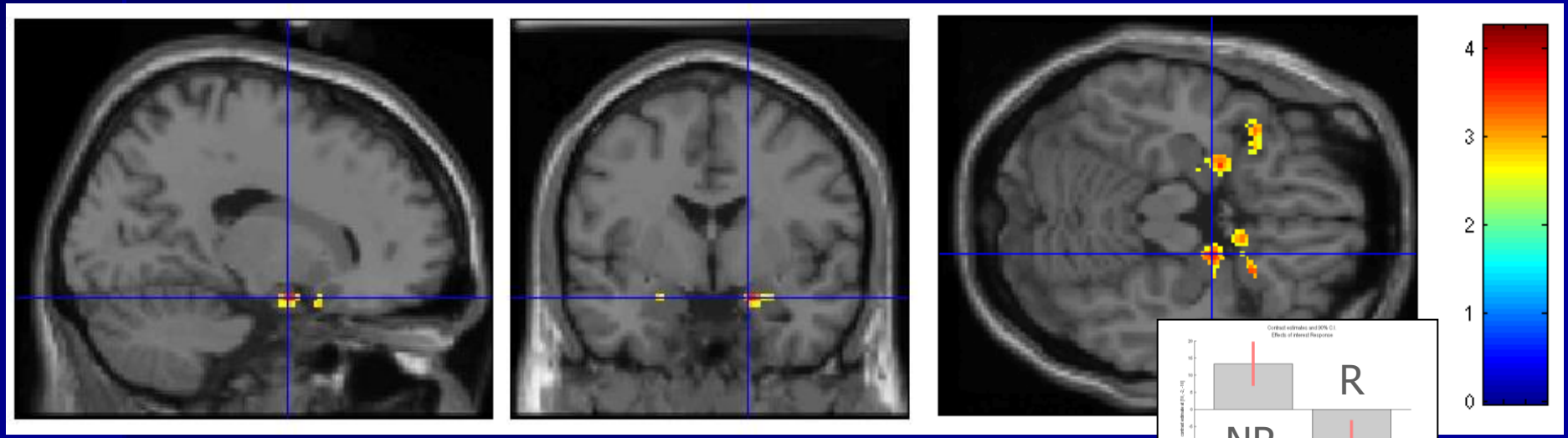
- Ruhé: Faces, PAR, n= 18, 12 wks
  - Response: 11/17 (65%)

Sheline et al. Biol Psychiatry 2001; 50:651-8
Davidson et al. Am J Psychiatry 2003;160:64-75
Fu et al. Arch Gen Psychiatry 2004;61:677-89
Robertson et al. J Clin Psychiatry 2007;68:261-7
Ruhe et al. J Clin Psychiatry 2012;73:451-9



Functional MRI
non-response vs. response

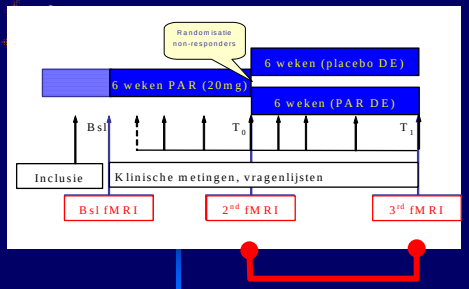
- Non-response > Response:



L+R Amygdala

– Indirect effect of antidepressant via response !!

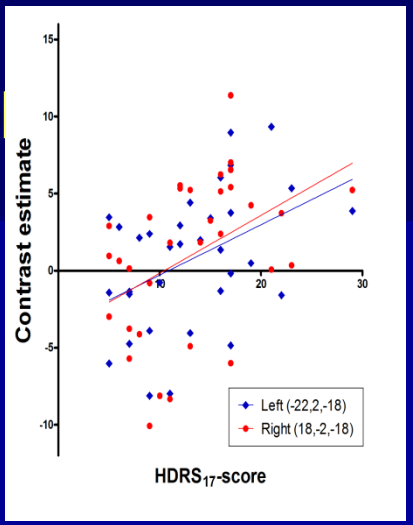
Ruhe et al. J Clin Psychiatry 2012;73:451-9

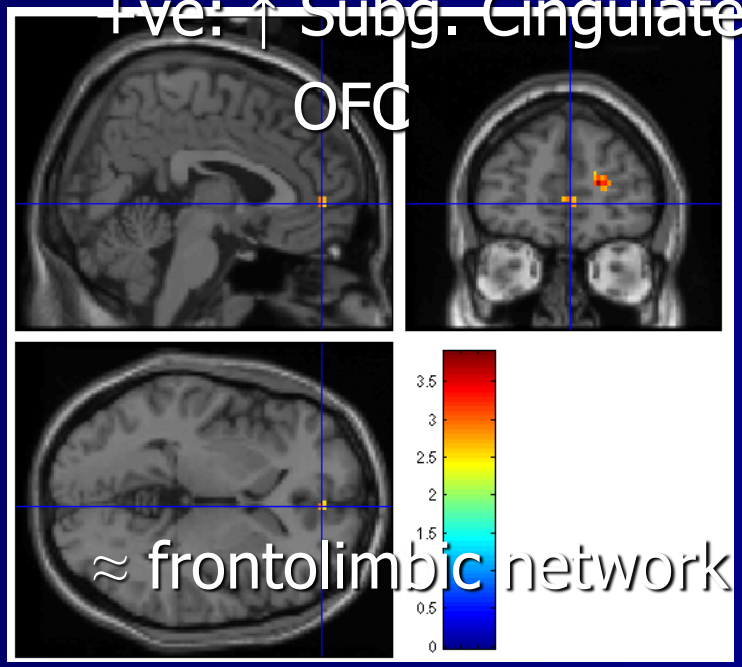


Functional MRI
non-response vs. respo

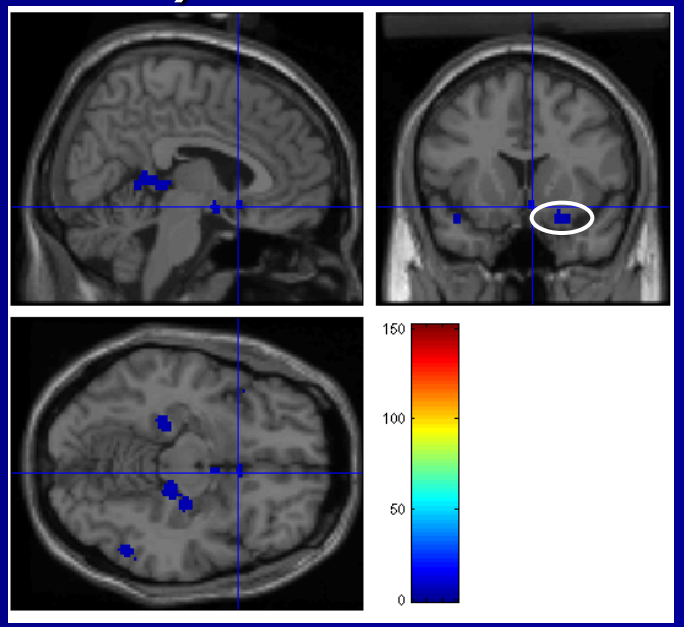
- Introduction
- Monoamine hypothesis
  - chemical
  - time lag
  - psychol.
- Beyond monoamines
- Networks
- Discussion

- Associations ↑ L. Amygdala act.
  - -ve: ↓ Preg. Cingulate (aCG24)
    ↓ DLPFC
  - +ve: ↑ Subg. Cingulate (aCG25)
    OFC





≈ frontolimbic network



Mayberg e.a. Br Med Bull 2003;65:193-207

Increased functional connectivity after 8wks FLX

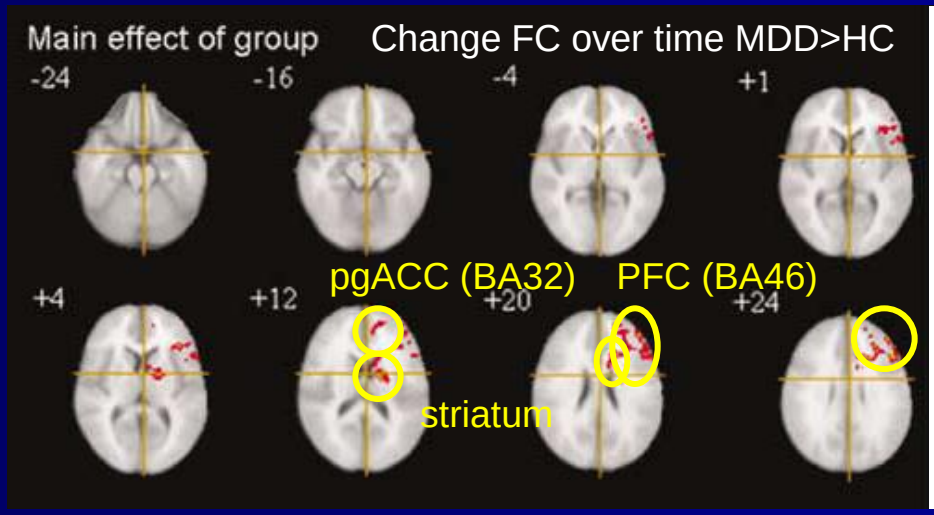
Introduction

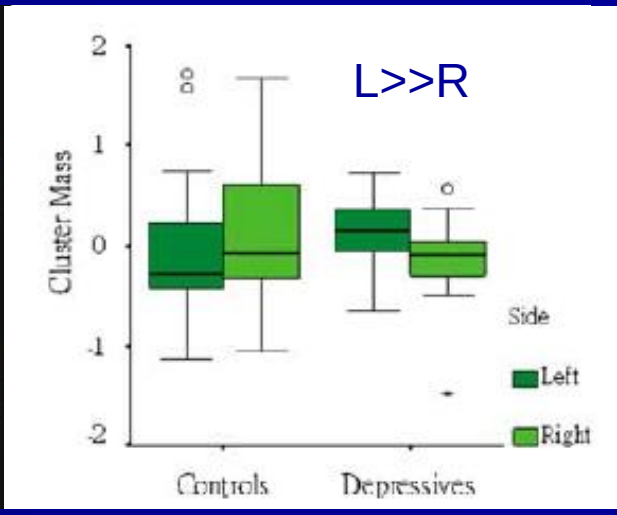
Monoamine hypothesis
- chemical
- time lag
- psychol.

Beyond monoamines

Networks

Discussion





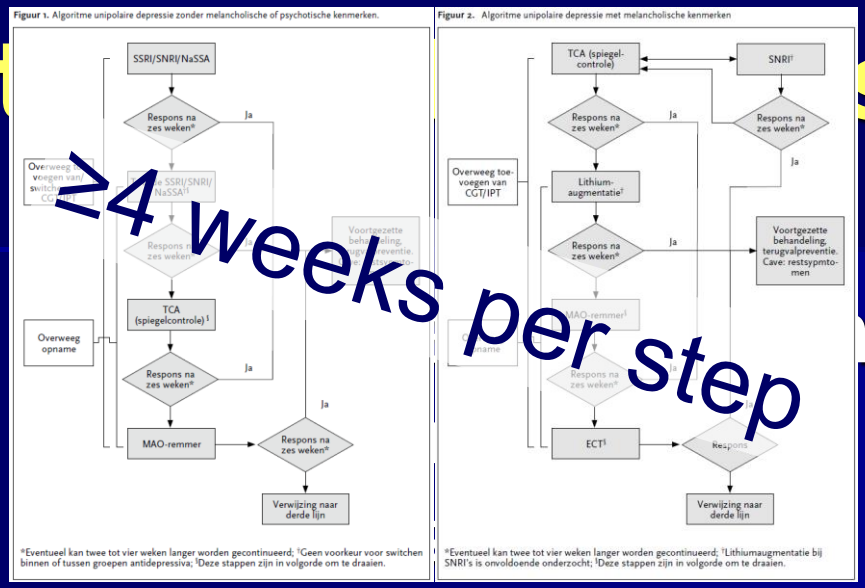
- MDD: FLX
- Controls: no treatment

- Seed region (bilateral amygdala) FC
- FC-changes over time x group

Chen e.a. Neuropsychopharmacol 2008;33:1909-18

Treat sion (unipolar)

- ts:



≥4 weeks per step

- One-size-fits-all approach
  - Doctor – patient preferences
  - Trial-and-change approach
- Could we instead predict outcomes
  - Pharmacotherapy or psychotherapy?
  - Which antidepressant will work?

The future

- We have good antidepressants
- But MDD is a heterogeneous concept
- We do not know who needs which treatment
- One-size does not fit all
  - Personalized medicine in reach??

Discussion

Acknowledgement

- Prof.dr. A.H. Schene, Prof.dr. R.A. Schoevers, Prof.dr. W.A. Nolen, Prof.dr. J. Booij, Prof.dr. P. de Jonge, Prof.dr. D.J. Veltman, Prof.dr. R.A. Dierckx, Prof.dr. A. Aleman, Dr. M.J. van Tol, Dr. M. Caan, Dr. J.A.C.M. Bastiaansen, Dr. L. Reneman, Dr. G. v. Wingen, Dr. A.H. Nederveen, Dr. M.W. Koeter
- Drs. M.M. Rive, Drs. R.J. Mocking, Drs. B.P. de Kwaasteniet, Drs. I.O. Bergfeld, Drs. H. Geugies, Drs. C.A. Figueroa
- G. van Rooijen, M. Koster, N. Mason, K.W. Ottenhof, S. Khoenkhoen, M. Groefsema
- Prof.dr. G. Goodwin & ECNP

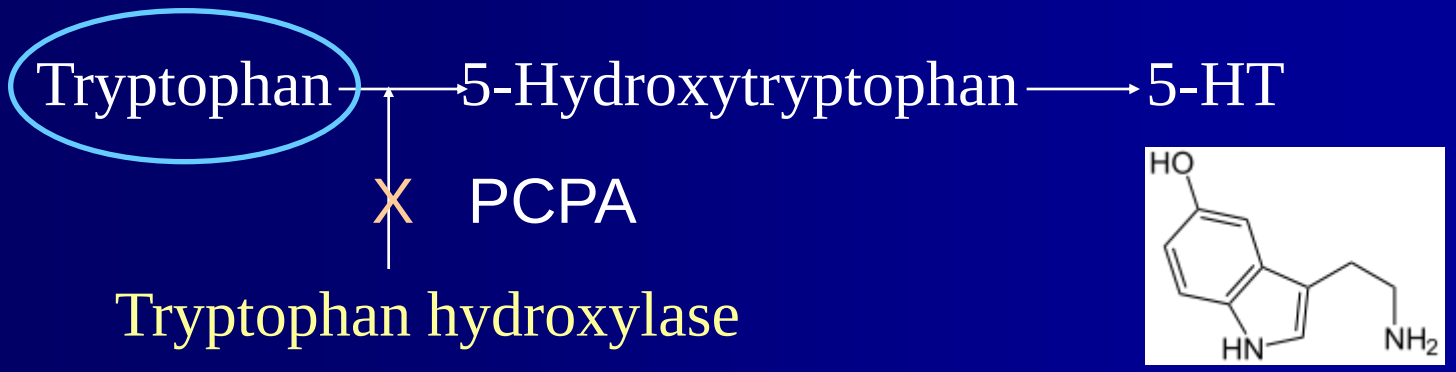

umcg

Roland Kuhn and the discovery of imipramine

"Forty patients were ultimately studied but the responses of the first three were so dramatic that the ward nursing staff and Kuhn had little doubt that the treatment was effective… Paula JF, who was depressed and deluded, started treatment on Jan 12th 1956 and six days later was completely transformed."

"The Antidepressant Era"
by David Healey, 1997

Synthesis of Monoamines

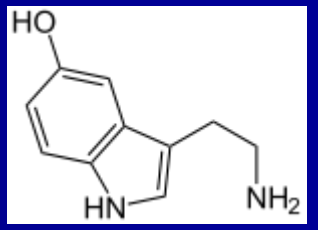


Synthesis of Monoamines

Tryptophan → 5-Hydroxytryptophan → 5-HT

X PCPA

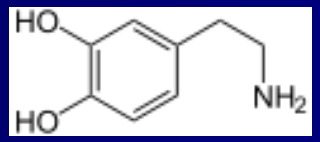
Tryptophan hydroxylase

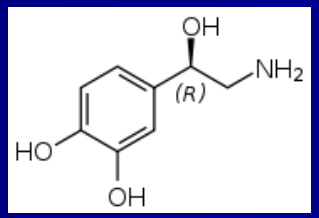


Tyrosine → Dopamine → Noradrenaline

AMPT X

Tyrosine hydroxylase



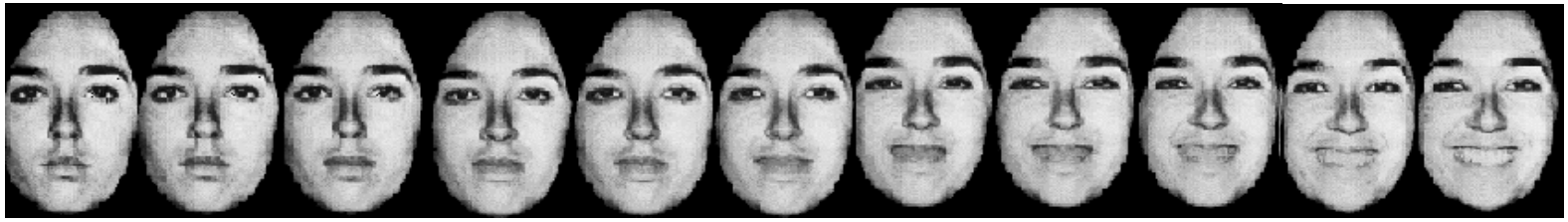


Facial Expression Recognition Task

Angry	Disgusted	Fearful	Happy	Neutral	Sad	Surprised

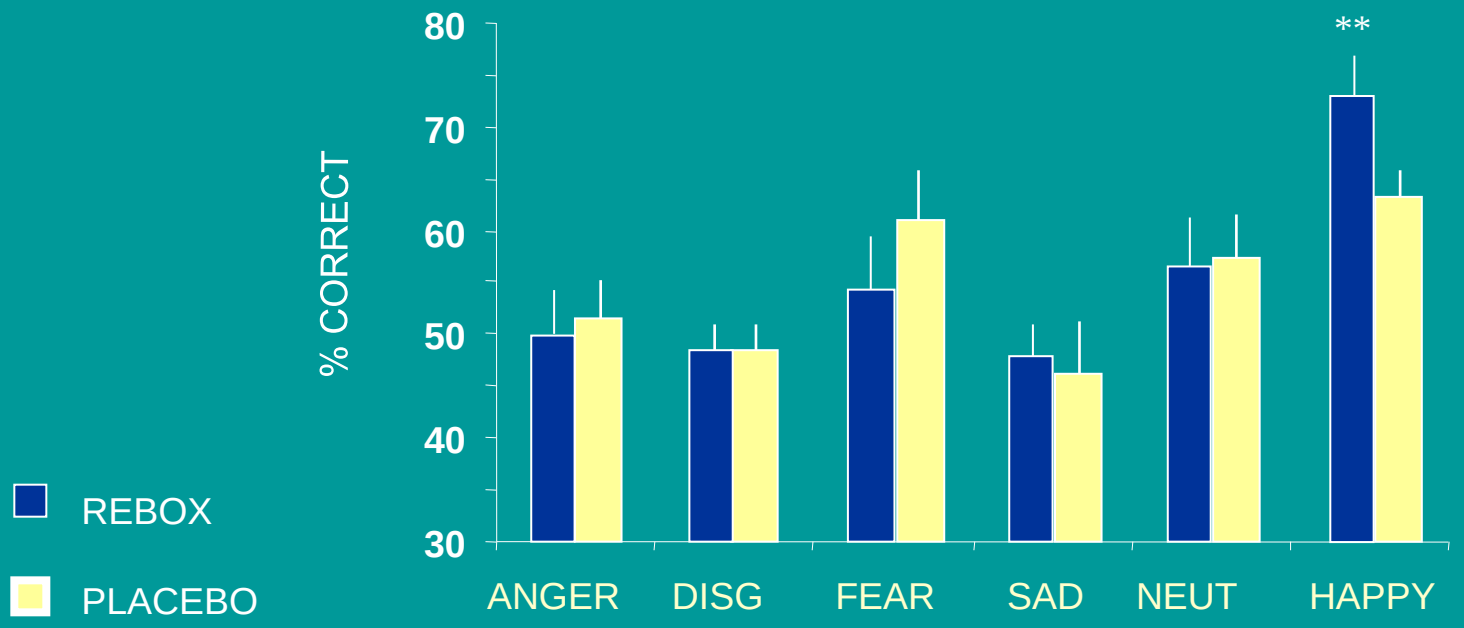
Courtesy of P. Cowen. ECNP School Neuropsychopharmacology 2010

Morphed faces



Courtesy of P. Cowen. ECNP School Neuropsychopharmacology 2010

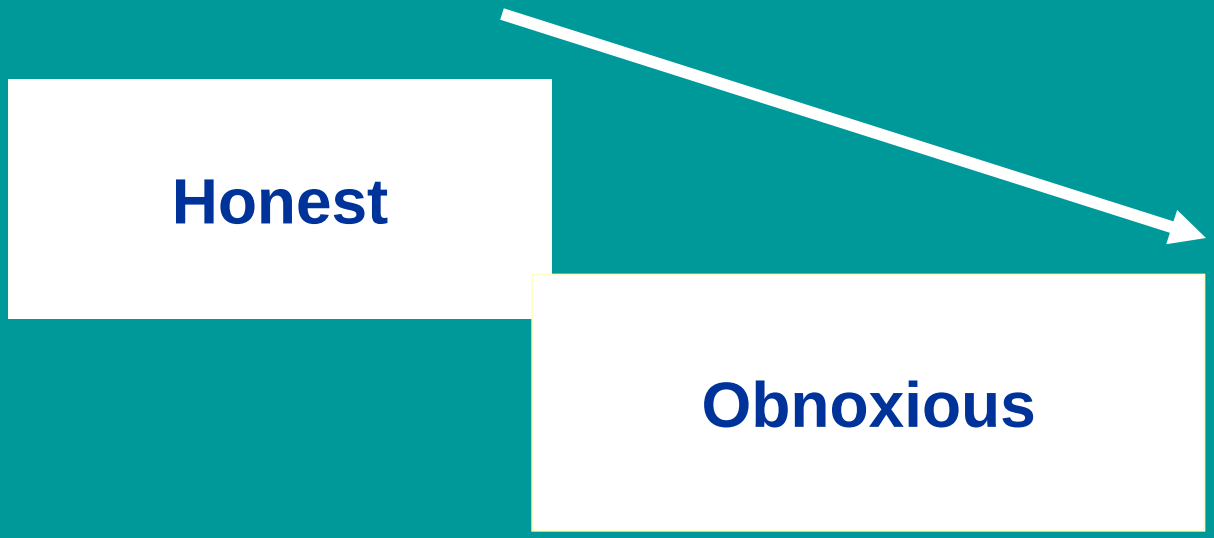
Facial expression recognition



• A single dose of reboxetine increased the perception of happy facial expressions in healthy controls

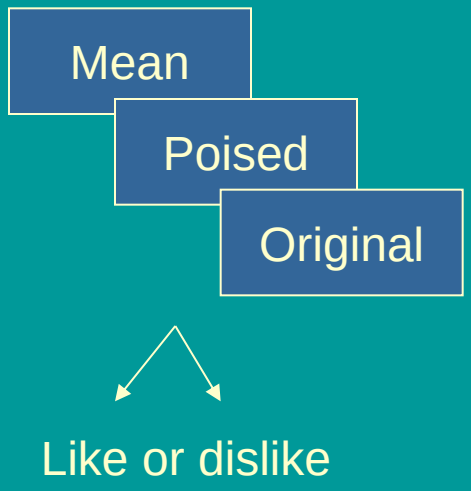
Courtesy of P. Cowen. ECNP School Neuropsychopharmacology 2010

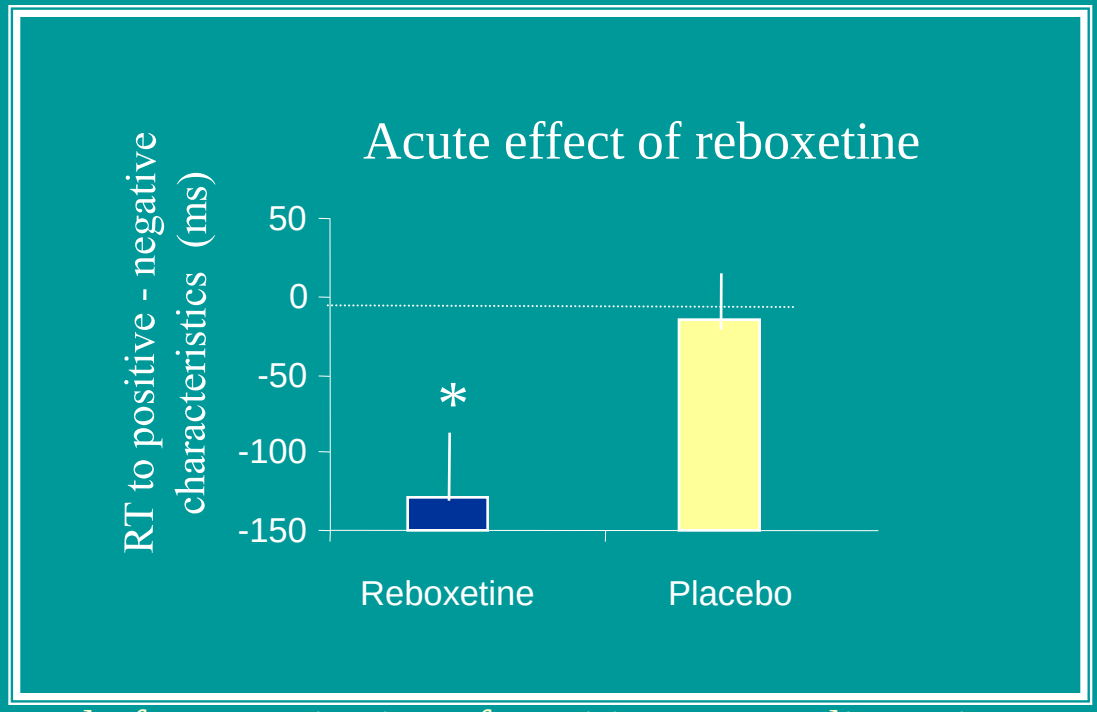
Emotional categorisation



Self:relevant: Would you be pleased or upset if you overheard someone referring to you as this characteristic?

Emotional Categorisation



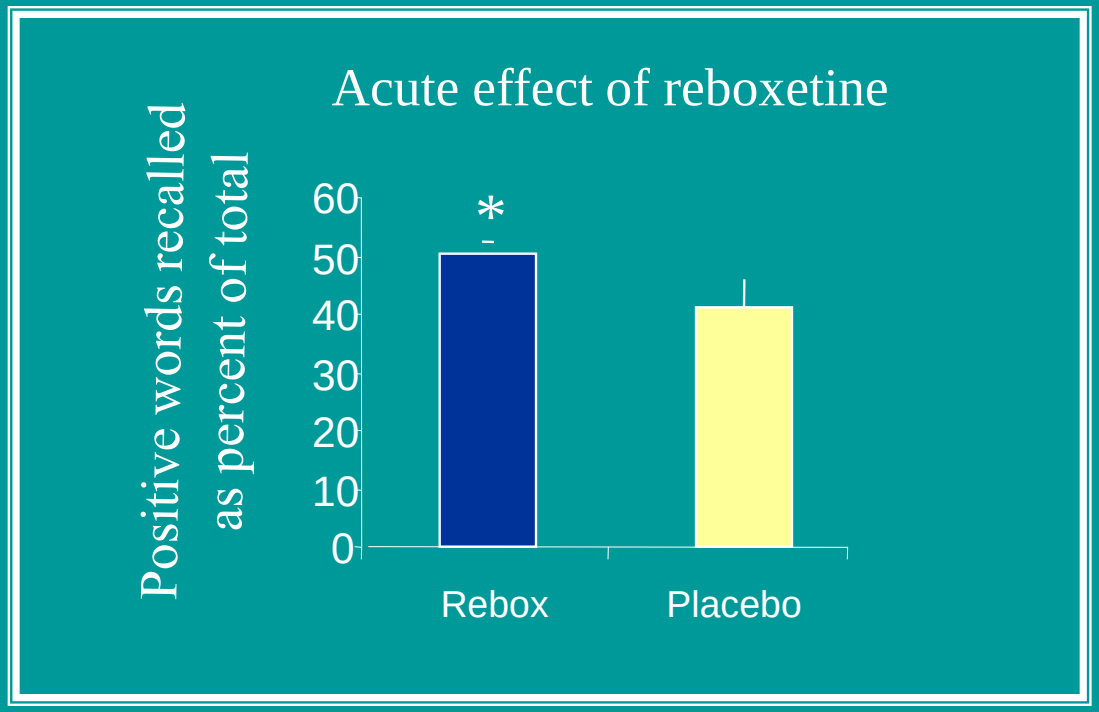


- The antidepressant facilitated speed of categorisation of positive personality traits increased in healthy controls

Emotional memory

- Surprise free recall of positive and negative personality characteristics

Emotional Memory



•Acute reboxetine increased relative memory for positive personality traits in healthy controls

Courtesy of P. Cowen. ECNP School Neuropsychopharmacology 2010

‘Diagnosis’ = Classification

- Major Depressive *Disorder*
  - √ 1 (or more) MDE
  - √ No manic, mixed or hypomanic episode
  - √ Not schizoaffective disorder etc.….

  Subtypes:
    - Severity & pychosis
    - Melancholic, atypical, catatonic features
    - First episode / Recurrent
    - Chronic / longitudinal course
- Bipolar Disorder I & II, most recent episode…
  - √ 1 (or more) (hypo-)manic episodes
  - √ Not schizoaffective disorder etc.….

  Subtypes
    - Severity & pychosis
    - Catatonic features
    - Longitudinal course
    - Cycling type

DSM-IV TR, 2000