# Bijsturing van de respons bij stress-stoornissen

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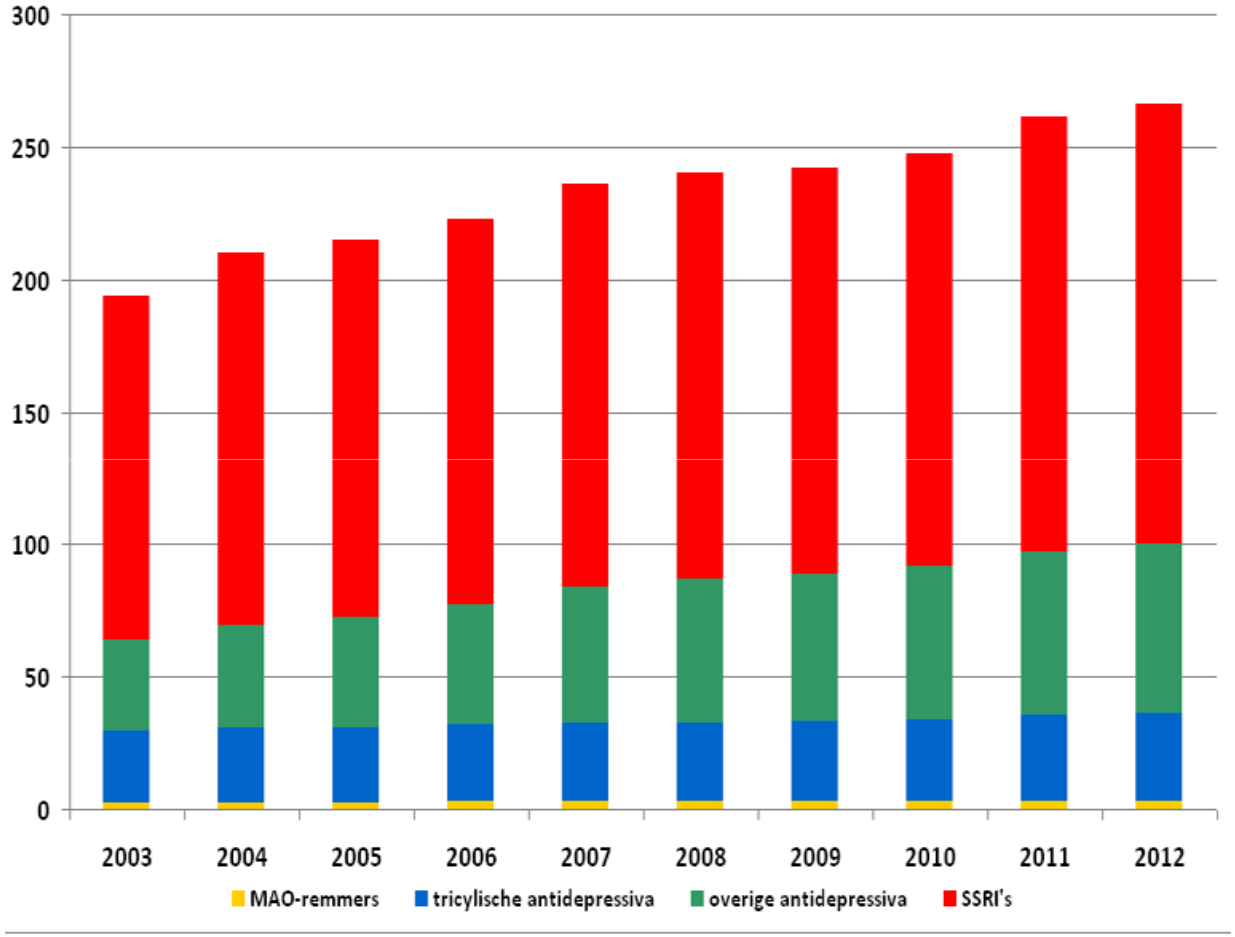
# Antidepressiva gebruik in Nederland




o.a. SNRI's
Agomelatine

*De stijging van het antidepressivagebruik van 2011 tot 2012 is van dezelfde orde als het gemiddelde van alle geneesmiddelgroepen.* **Bron: Stichting Farmaceutische Kengetallen**

# Monoamine theory of depression

SSRI's

TCA's

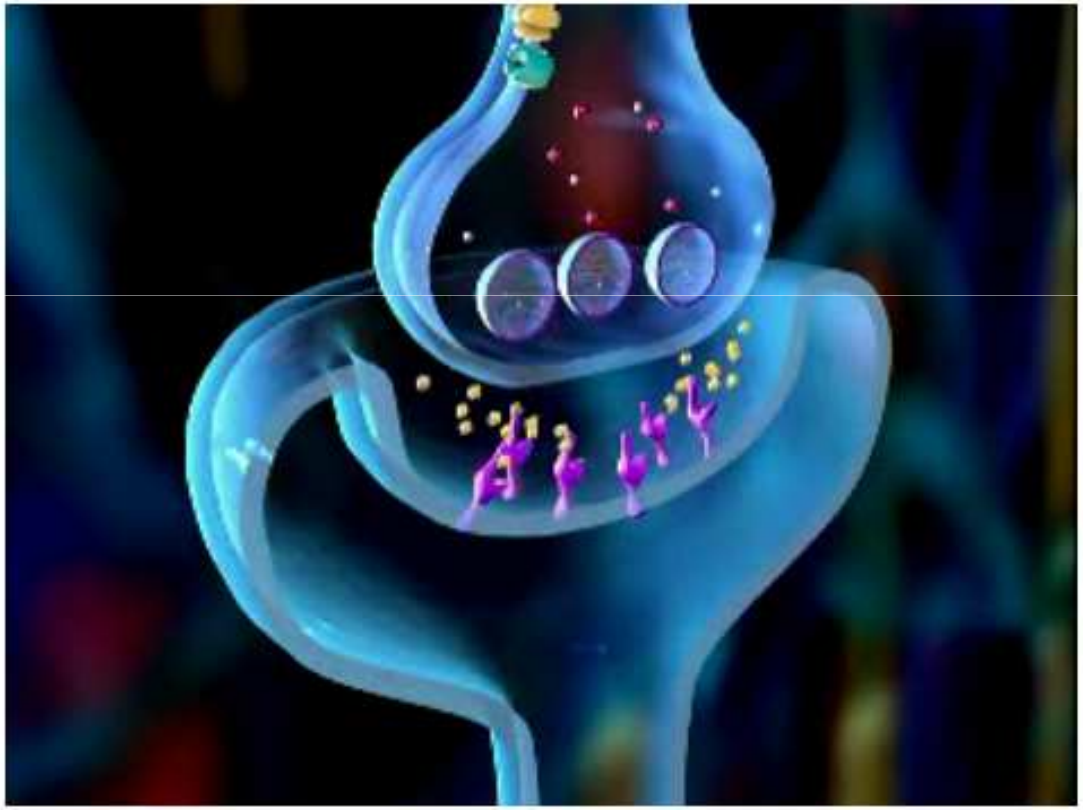
MAO-Inh



improvements

The Causes and Effects of Depression

Depression is a treatable illness caused by a decrease in neurotransmitter levels. Here's more information on the causes, effects, and treatment of depression.



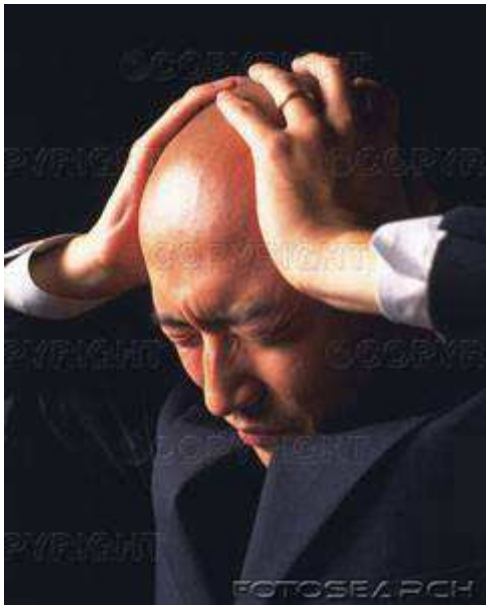
# Stress en psychopathologie

Stress

CRH

AZS

HPA axis

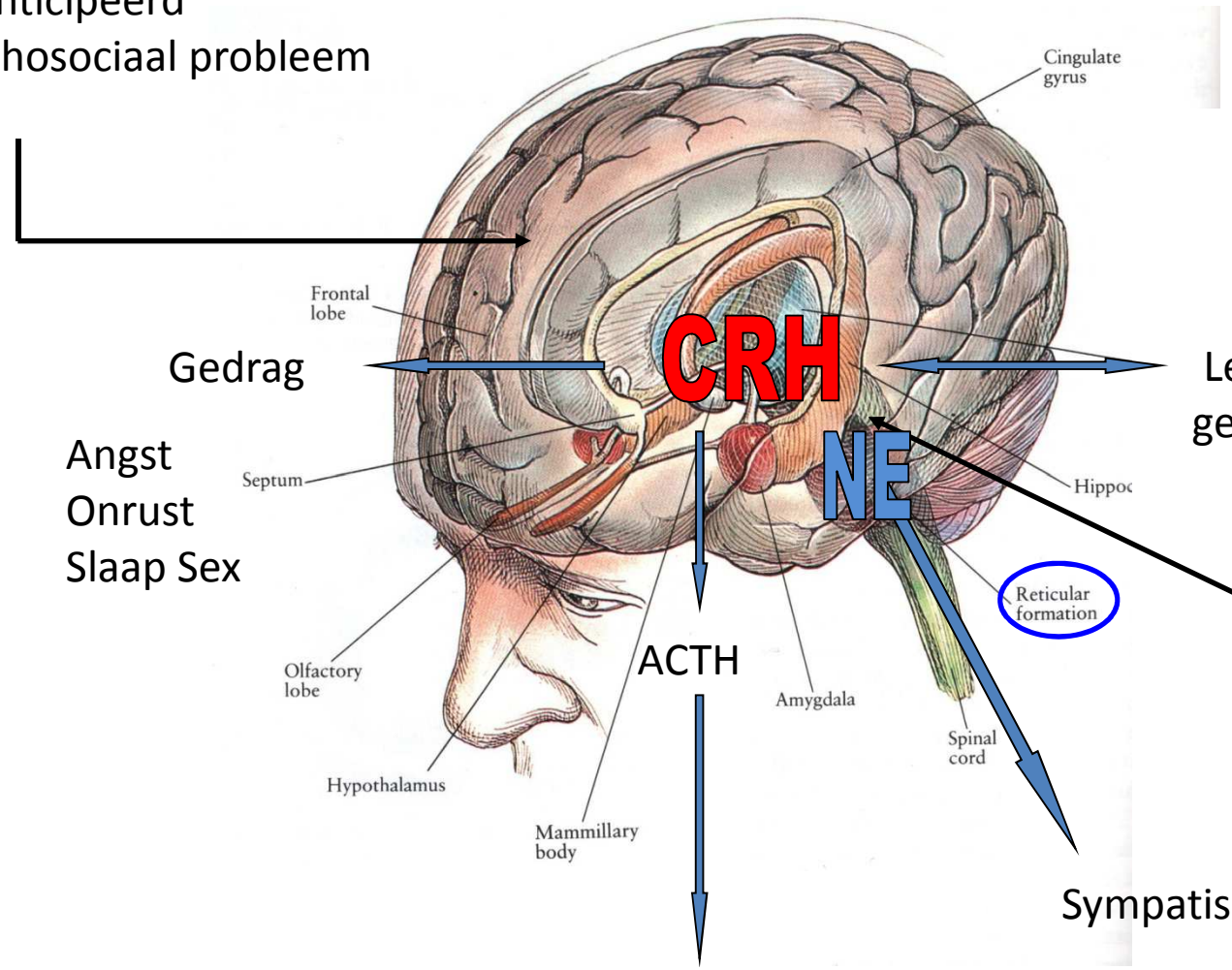


Precipitatie psychopathologie

Is het mogelijk, met de huidige kennis van stress, een nieuw medicament te ontwikkelen

# De snelle initiele stress-respons

Geanticipeerd
psychosociaal probleem




Gedrag

Angst
Onrust
Slaap Sex

Leren en
geheugen

Fysiek

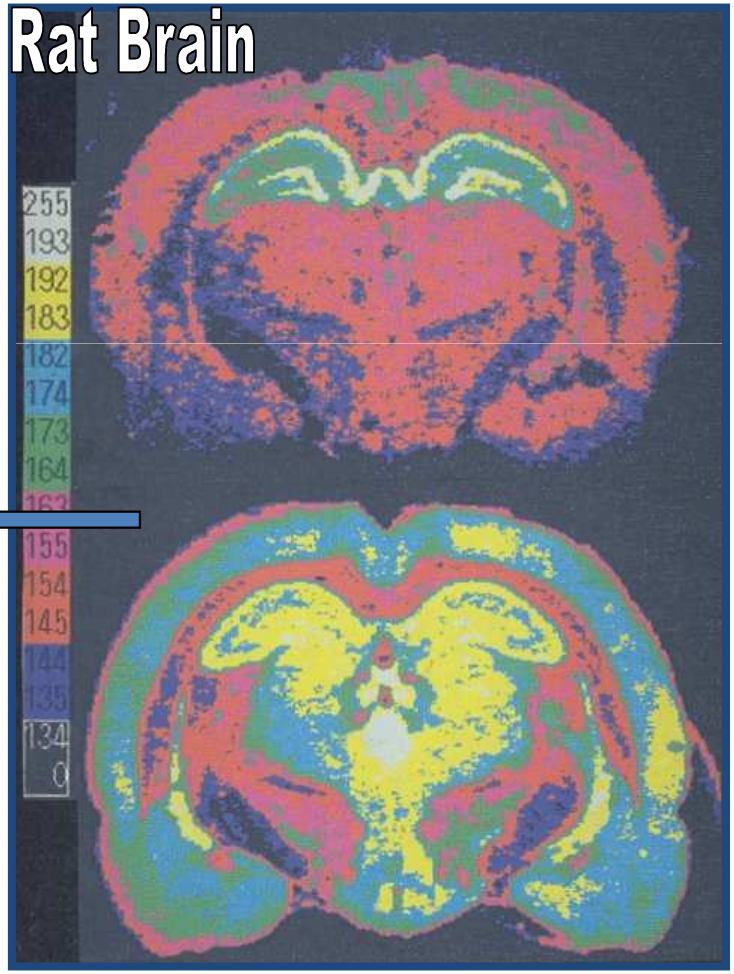
Immunologisch

ACTH

Sympatische activiteit

Cortisol

# Corticosteroid receptor diversiteit: MR and GR in het brein




HPA as regulatie

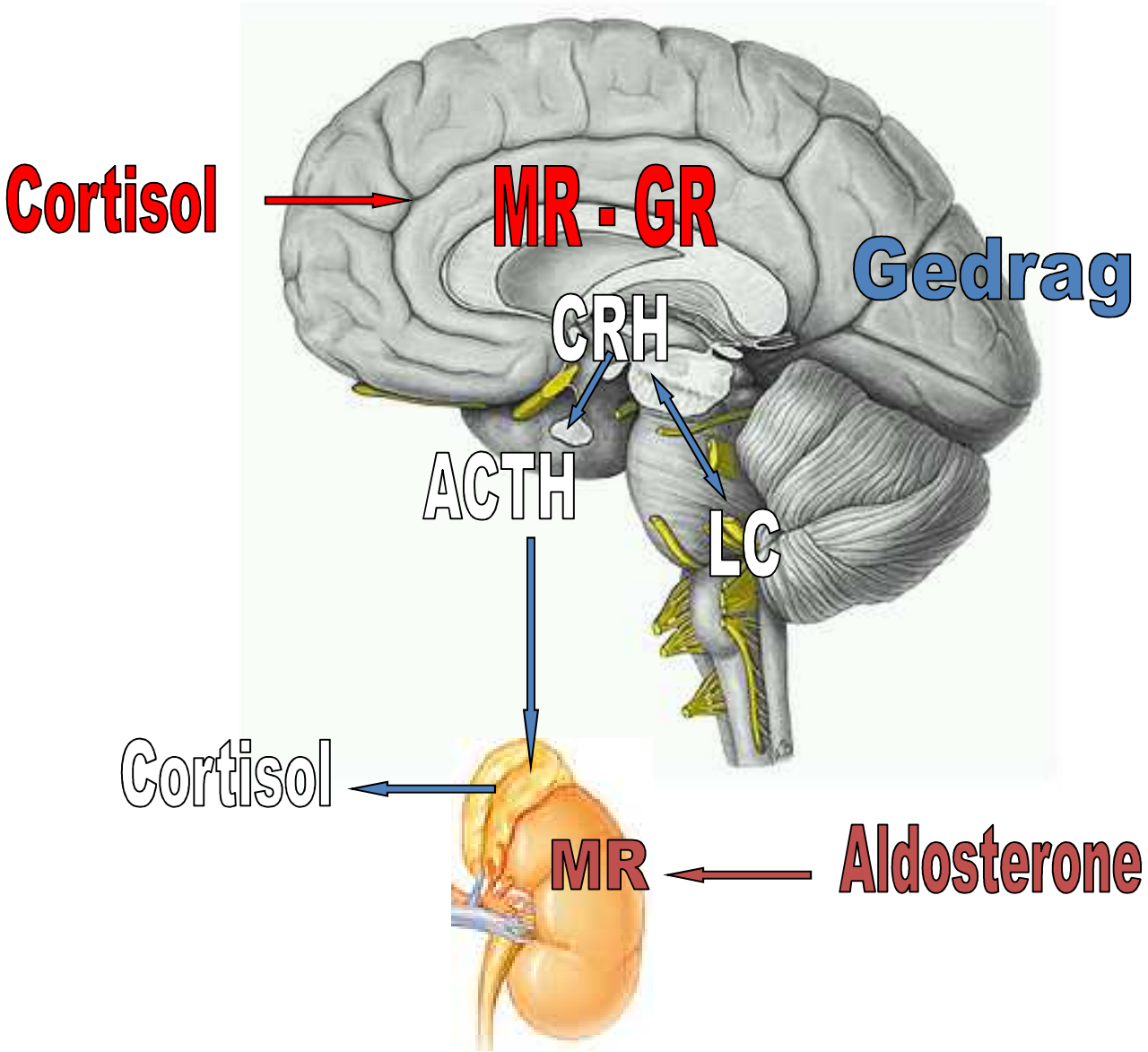
Gedrags adaptatie

*'Mineralocorticoid' Receptor*
* hoge affiniteit
* discrete lokalisatie
* Hoge bezetting met cortisol

*Glucocorticoid Receptor*
* 10x lagere affiniteit
* overal
* Bezet na stress

**Reul/de Kloet 1985**

# Mineralocorticoid receptoren in de stress-respons en electrolyt regulatie



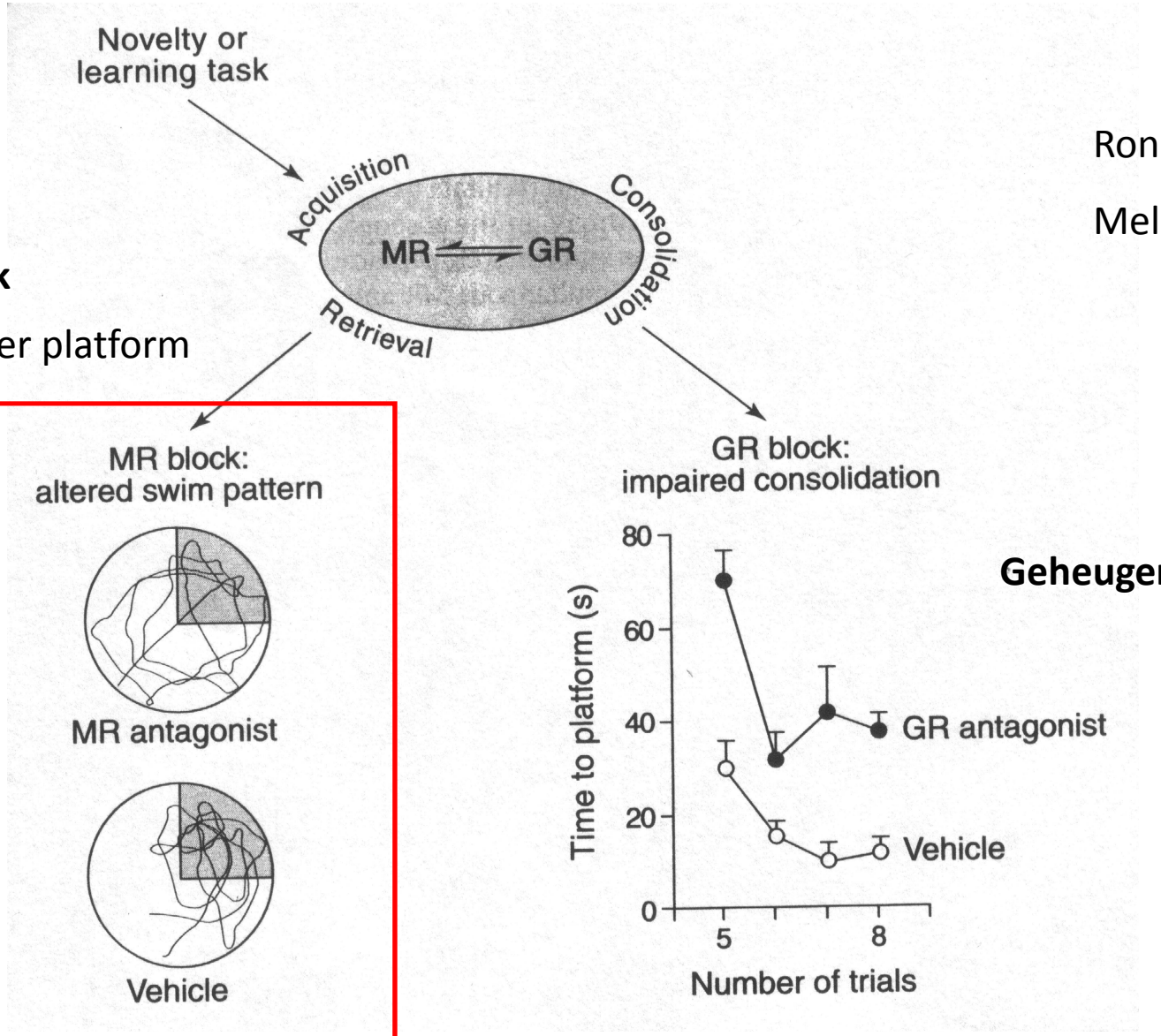
# MR en perceptie: muizen

Ron de Kloet

Melly Oitzl

**Gedrag's dynamiek**

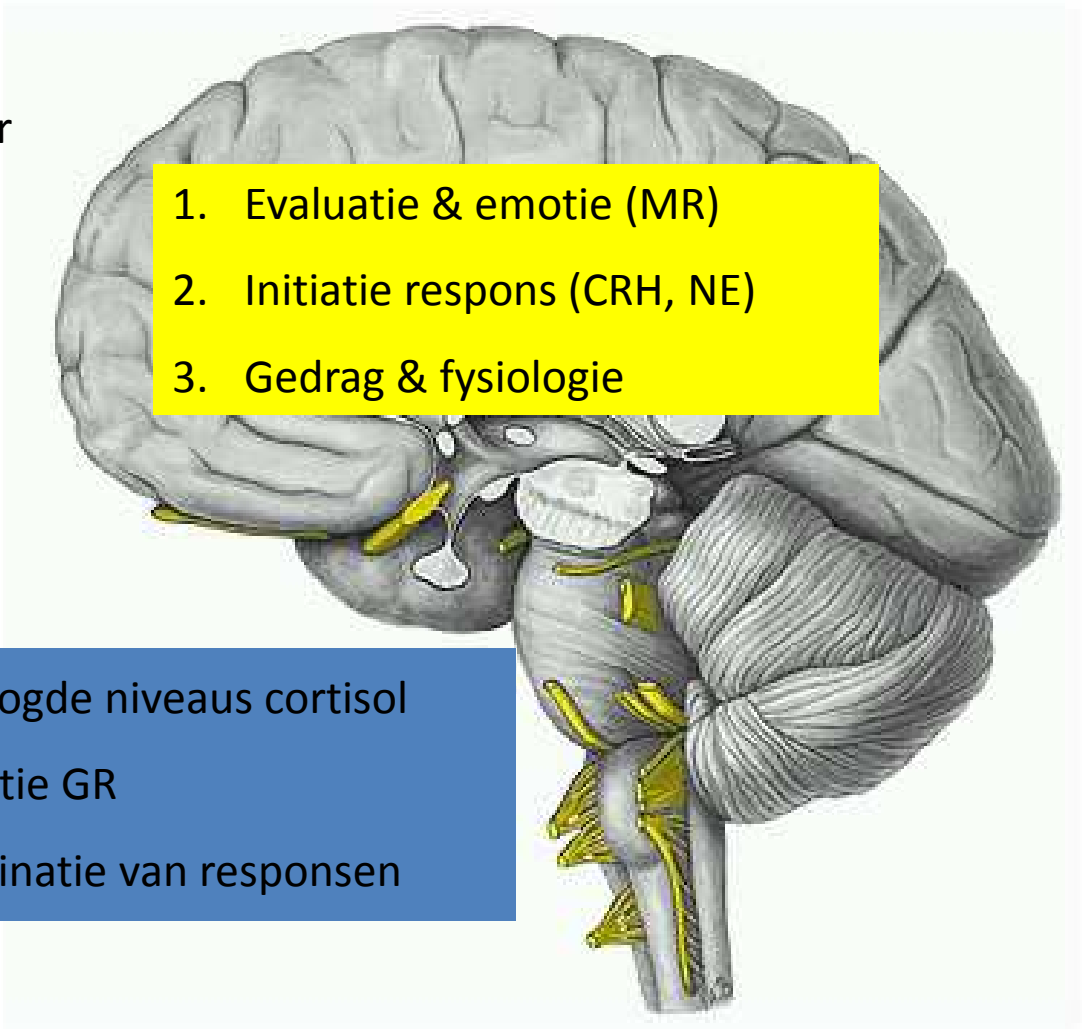
Test: zonder platform




**Geheugen**

# Stress-respons maakt adaptieve actie mogelijk

Stressor



1. Evaluatie & emotie (MR)
2. Initiatie respons (CRH, NE)
3. Gedrag & fysiologie

4. Verhoogde niveaus cortisol
5. Activatie GR
6. Coordinatie van responsen

## Hypothese:

Functionele genetische variantie van het MR-gen:

1. Determinant van de stress-respons
2. Kwestbaarheids factor

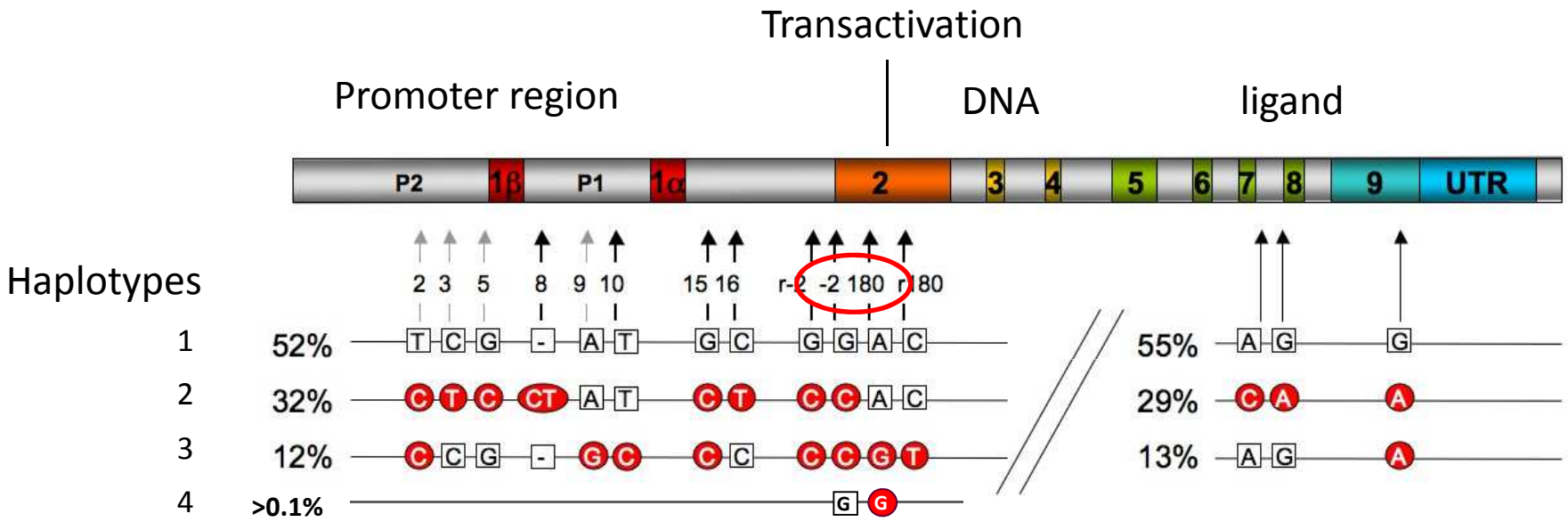
## De “candidate gene approach”:

1. Breng  humane genetische variatie in kaart
2. Karakteriseer genetische variatie in vitro
3. Specifieke in vivo testen

## Approach:

1. Search for human MR-gene variants and haplotypes
2. Test functionality *in vitro*:
3. Cardiovascular regulation
4. Neuro-endocrine effects in healthy subjects
5. Behavior in healthy subjects
6. Association with psychopathology

# MR-gene SNPs and haplotypes




Sequencing 50 anonymous subjects:

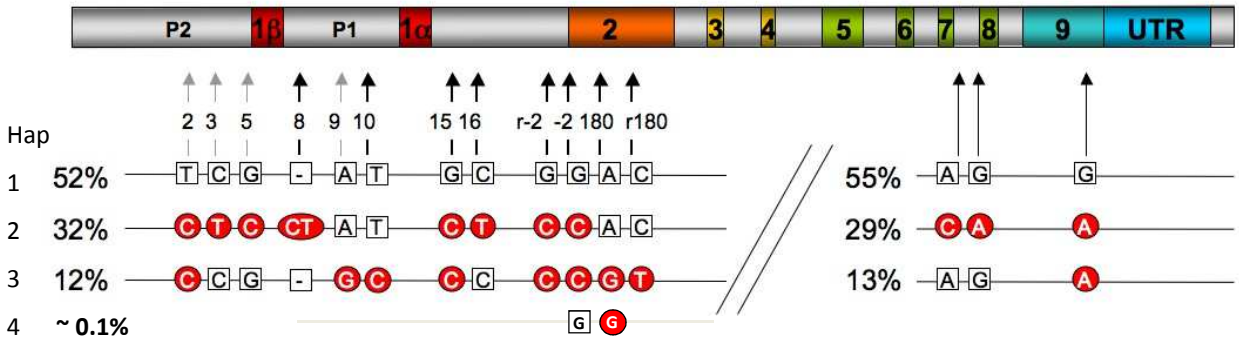
5’ promotor, exons & 3’ UTR regions

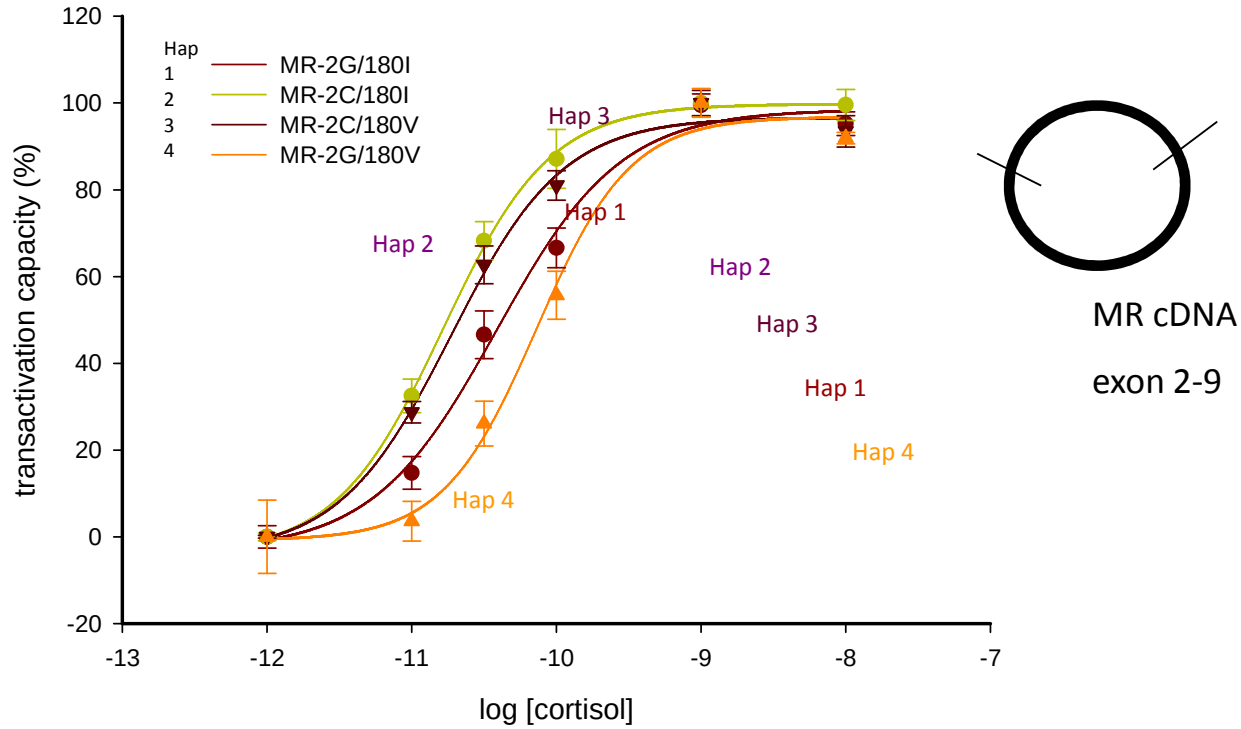
-2 G/C

I180V

DeRijk / van Leeuwen / Klok

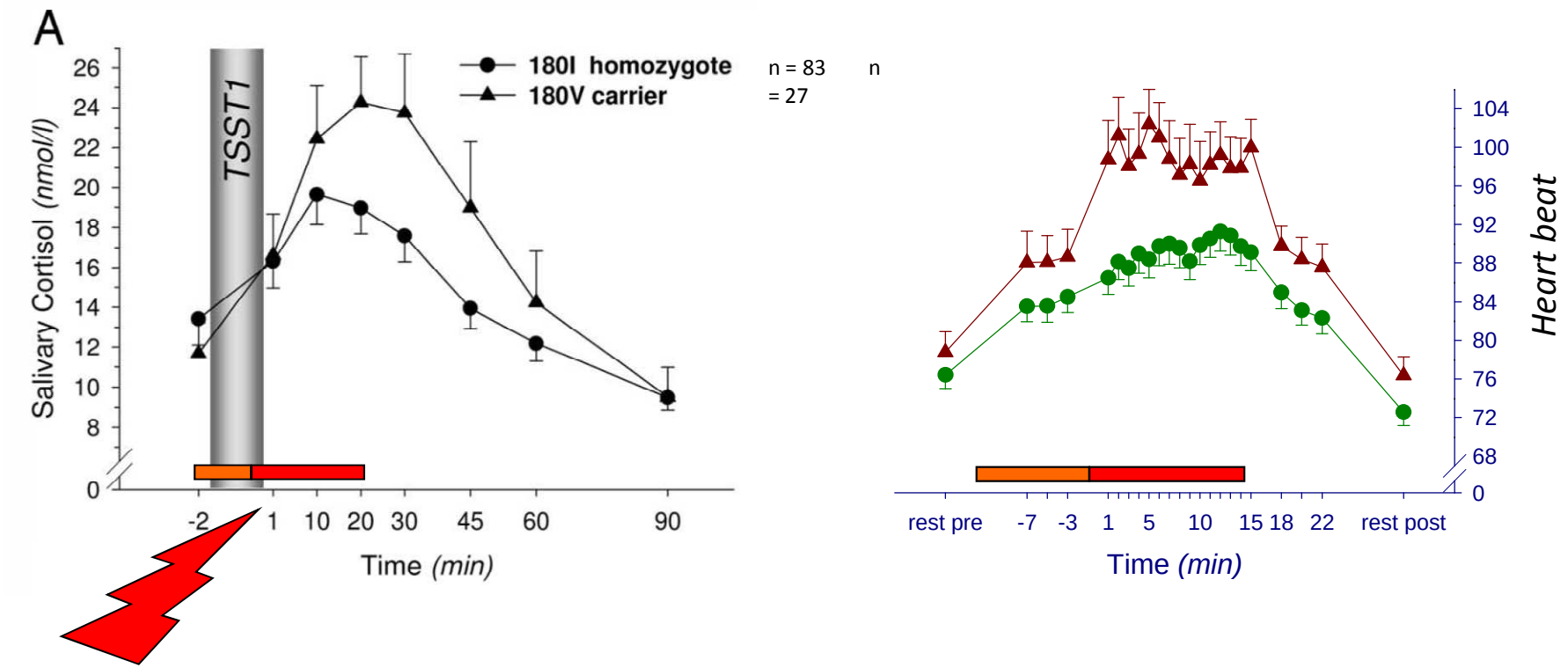
# Human MR-haplotypes are functional different




van Leeuwen, Klok, submitted

# Verhoogde cortisol and autonome responsen tijdens de TSST in dragers van de MR180V



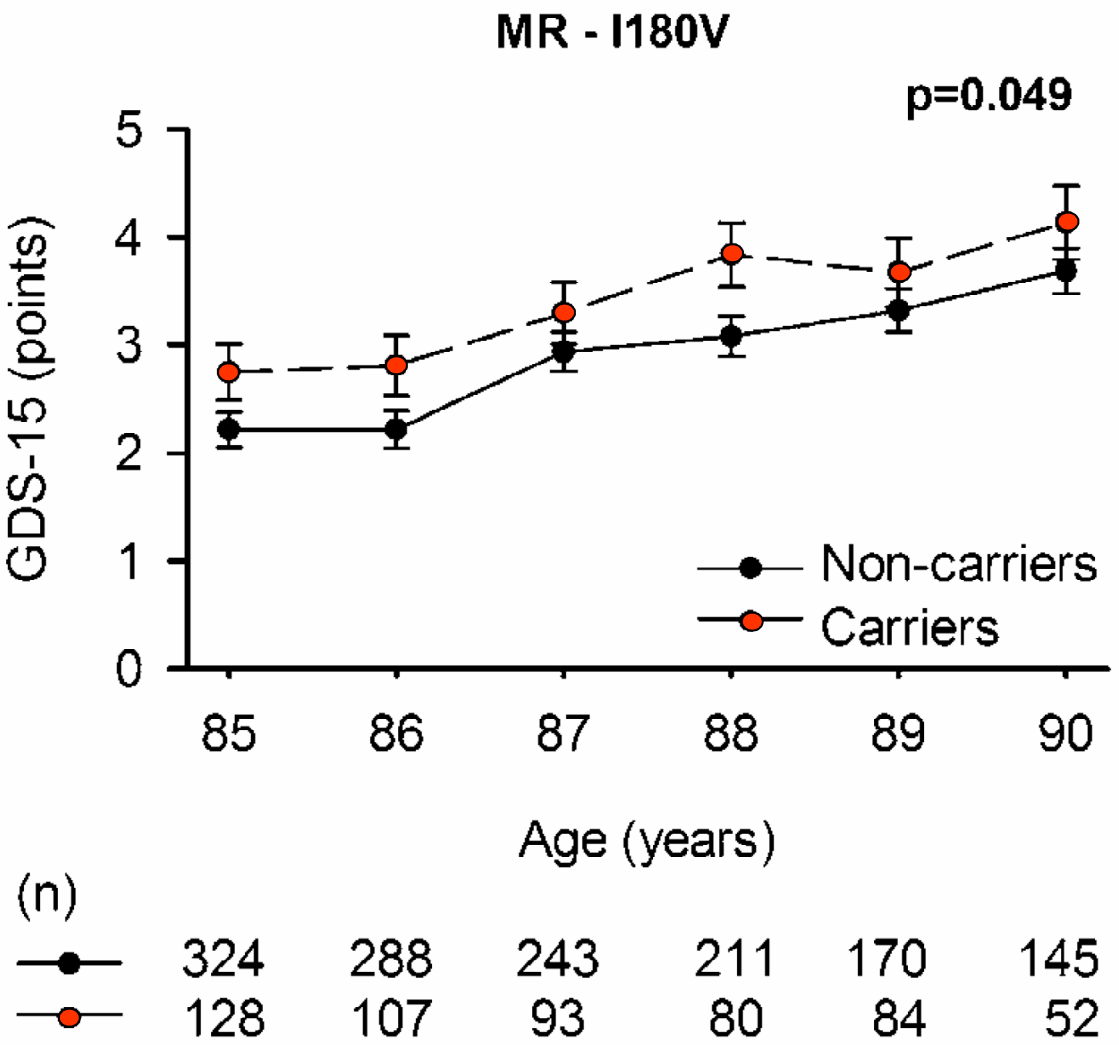

Preparation speaking Mental arithmatic

Public

GR-SNPs are not confounding MR effects

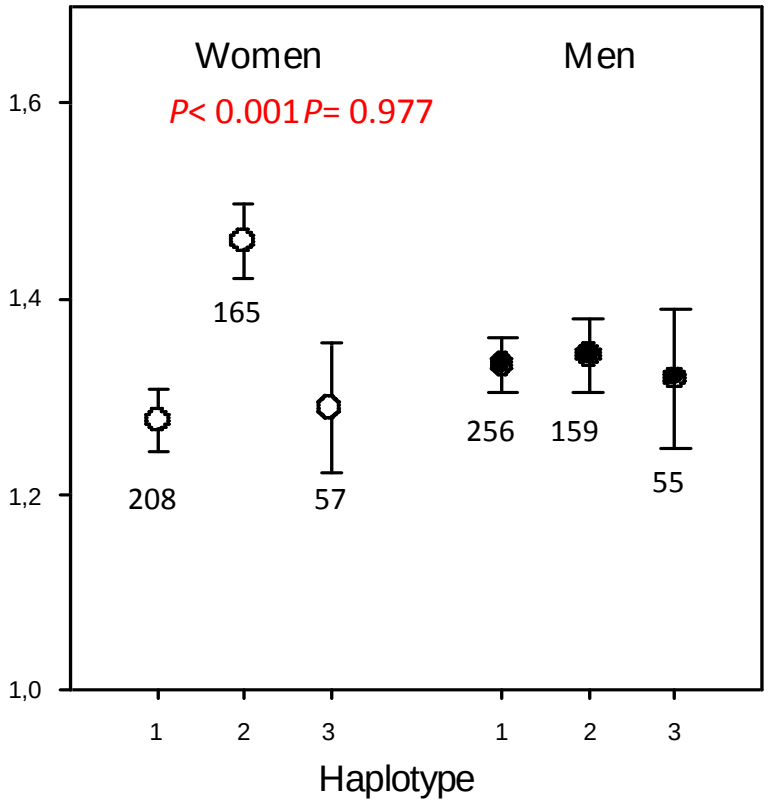
DeRijk / Wüst 2006 JCEM

# MR I180V is associated with feelings of depression in the elderly




Kuningas, DeRijk; NeuroPsychopharmacology 07

# Gender dependent association between MR haplotype 2 and optimism

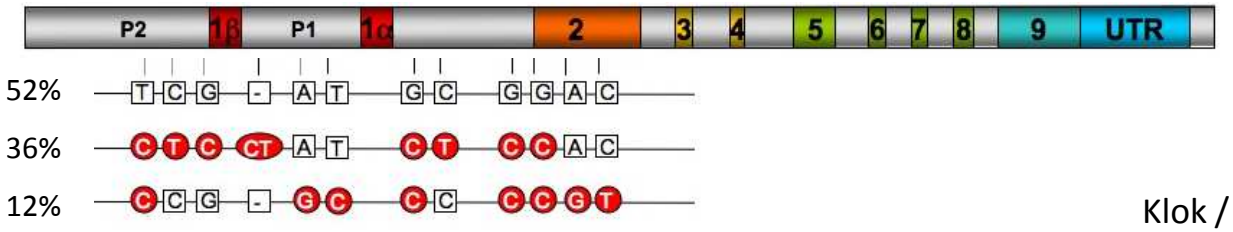



Association in elderly cohort from Arnhem

Overall mean optimism

Females: 1.35

Males: 1.34

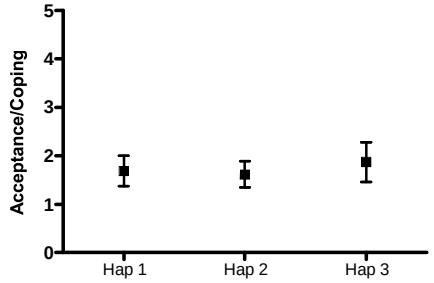



Klok / Giltay et al; submitted

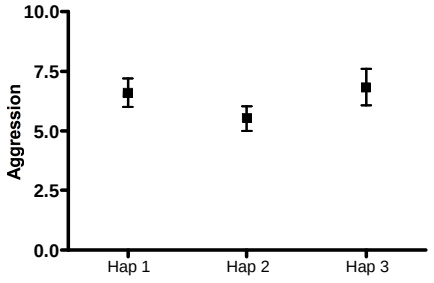
# LEIDS-R subscales in female students

## questionaire cognitive reactivity

Acceptation / coping



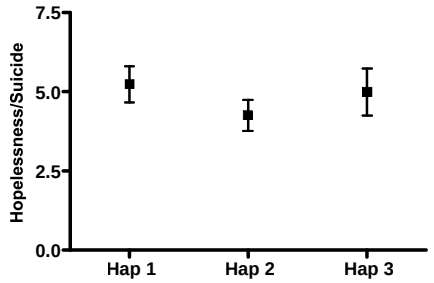

Scale 0-20



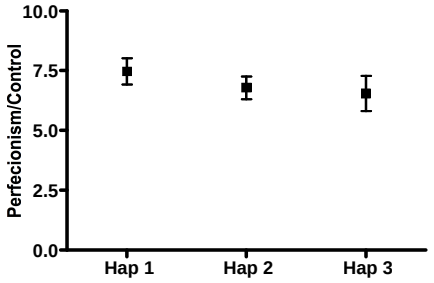

Scale 0-24

Aggression

Hopelessness



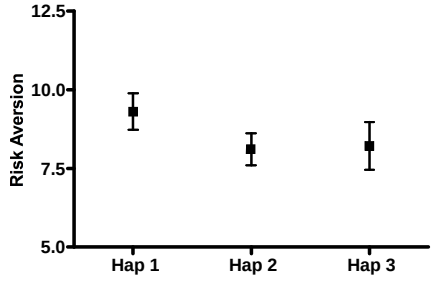

Scale 0-20



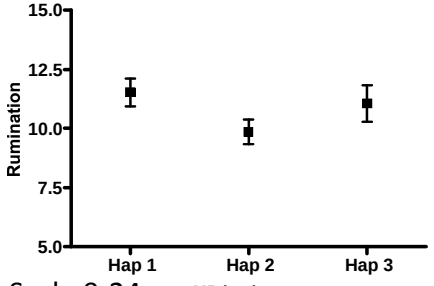

Scale 0-24

Perfectionism

Risk aversion




Scale 0-24



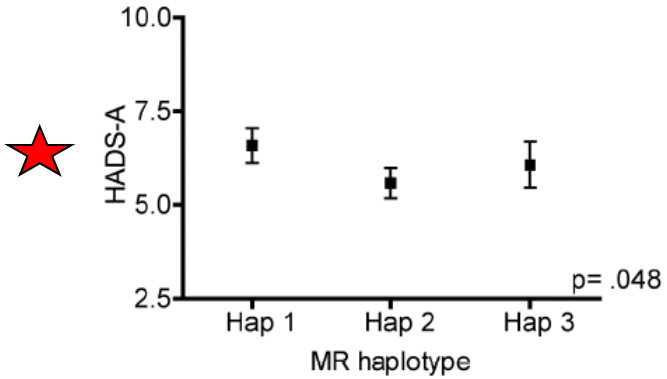

Scale 0-24

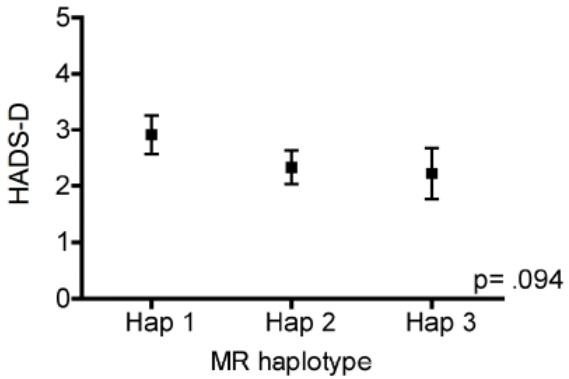
Rumination

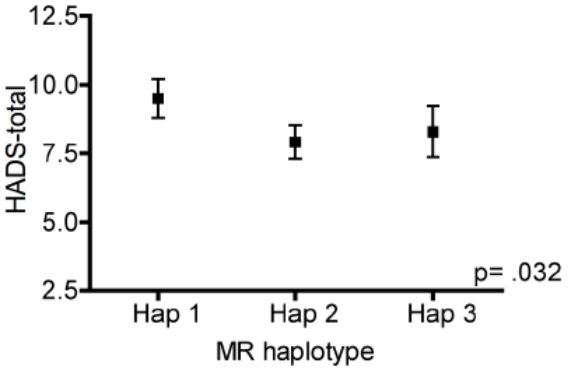
**Totaal (n= 140)**

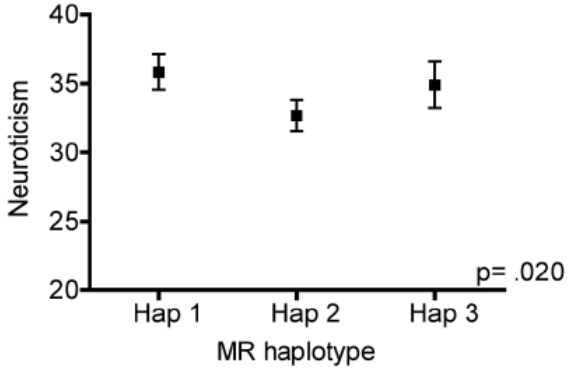
Klok, van der Does, submitted

# LEIDS-R subscales in female students



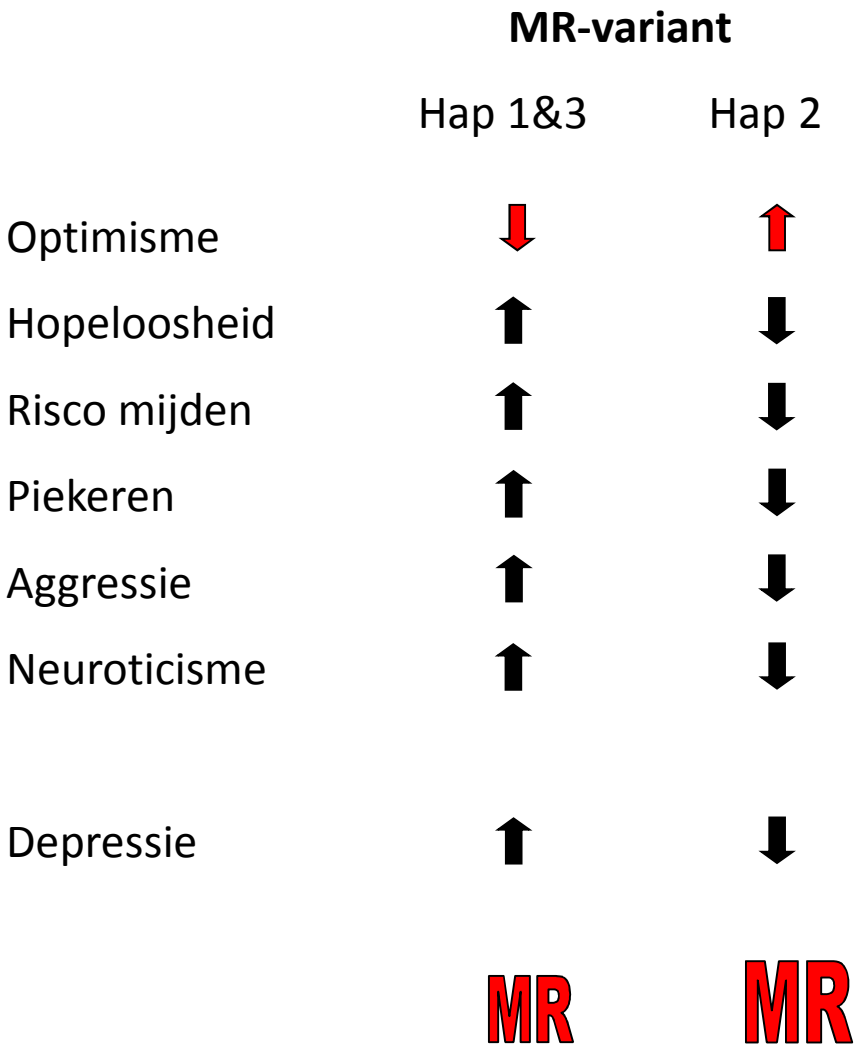



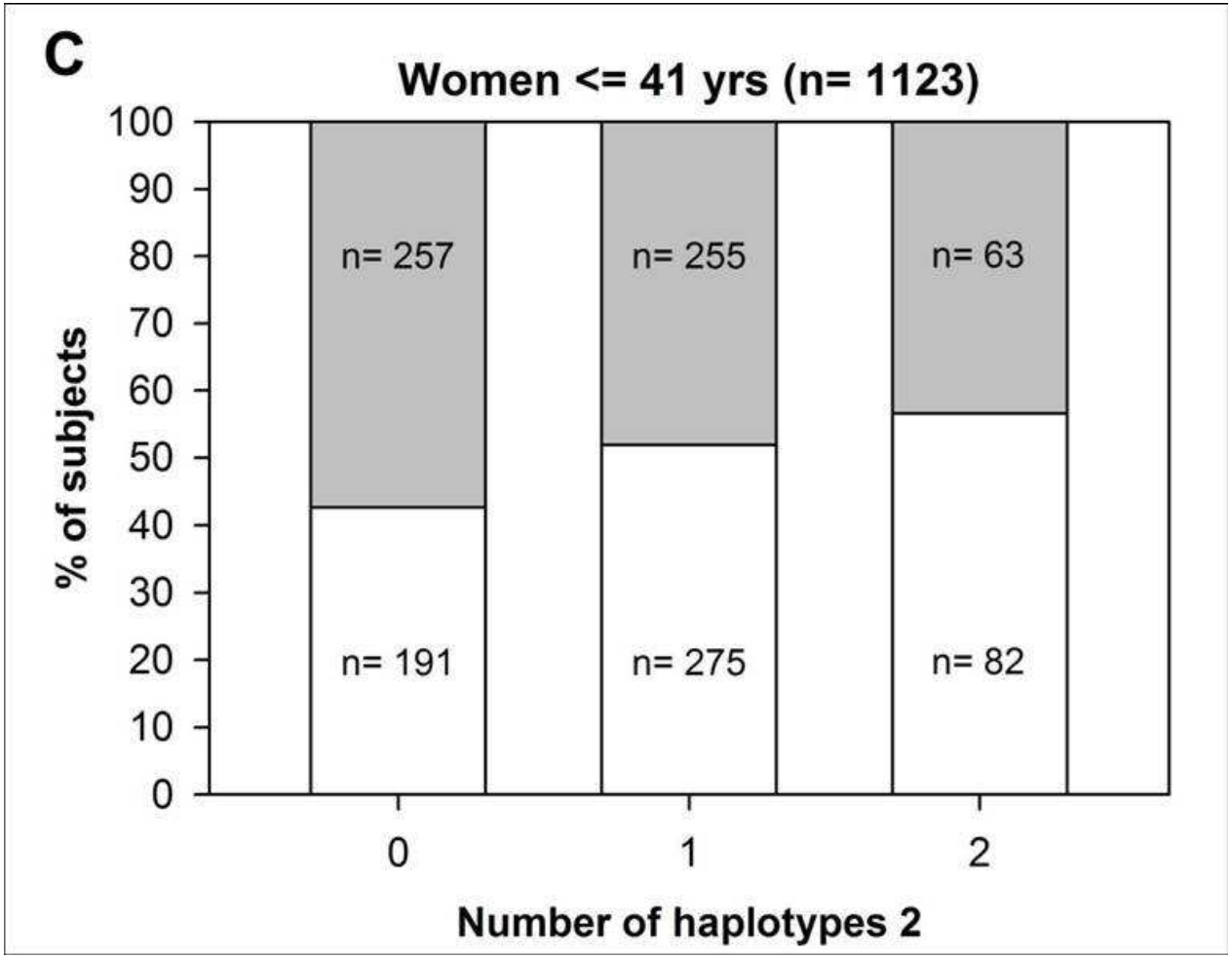




MR-gene variants → behavioral endophenotype / depression

# Effect van genetische variatie in MR



# MR Hap 2 associates with less depression




Healthy controls

Patients

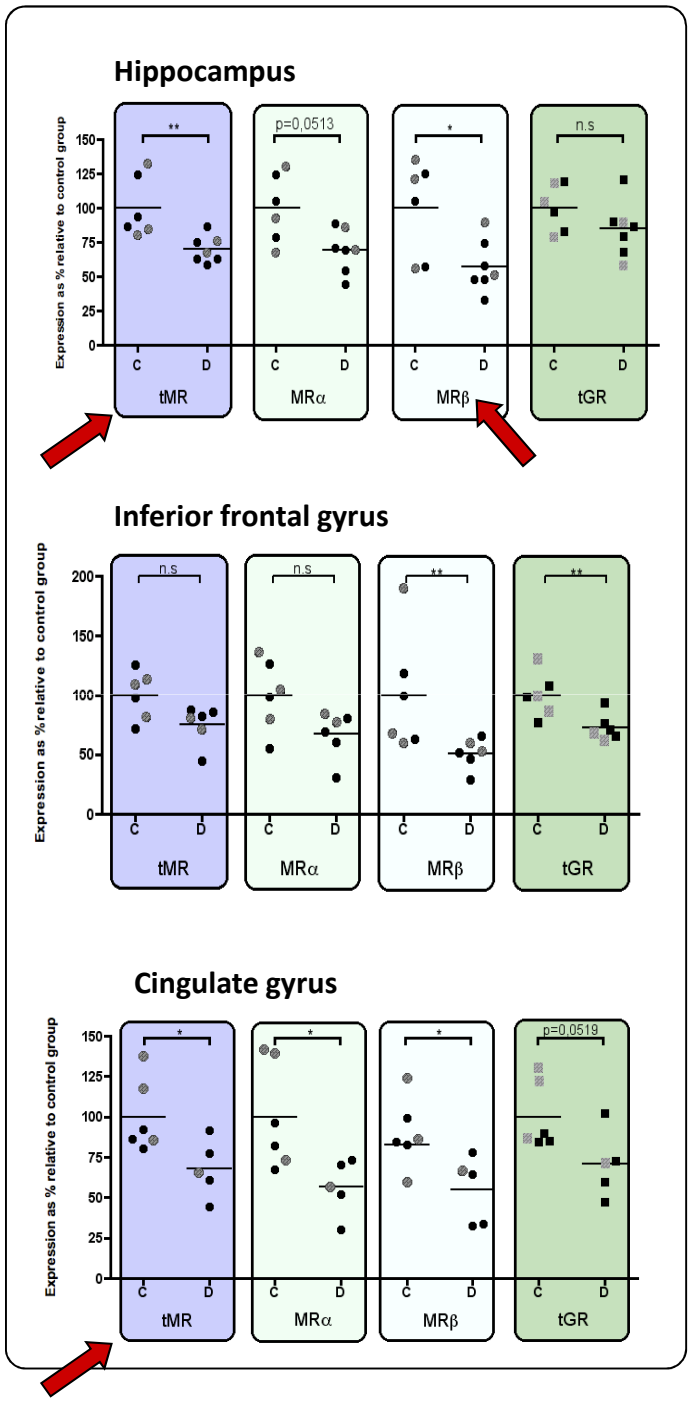
Klok / DeRijk Submitted

# MR expression in depression?

Hypothesis: lower MR in depression

Q-PCR study, postmortem brain tissue

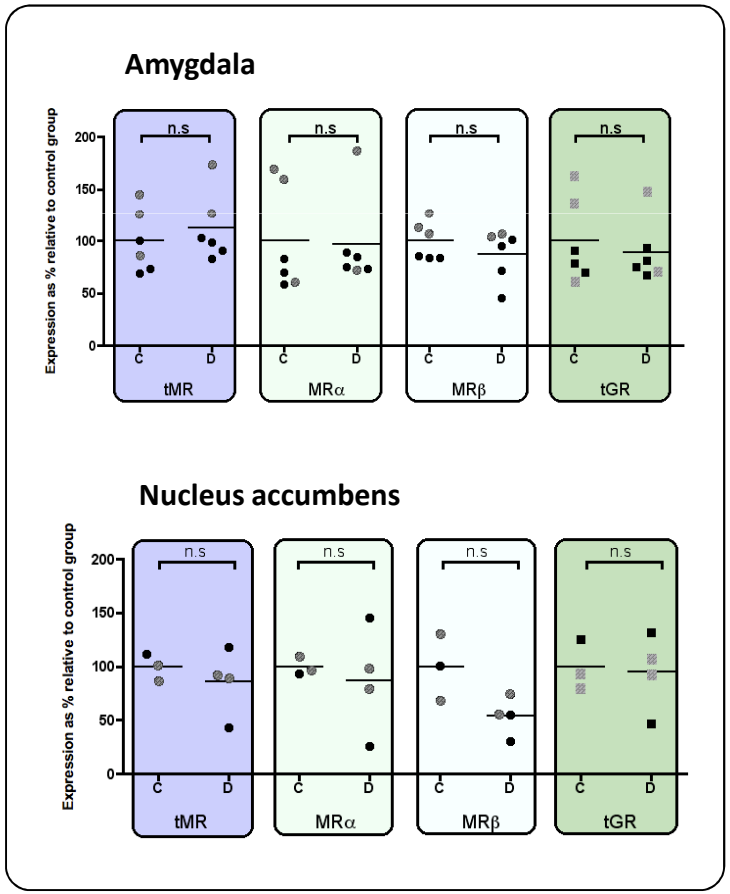
mRNA of MR, GR, exon1$\alpha$ MR and exon1$\beta$ MR




# MR-expression:

# controls vs. depressed

MRβ role in neuronal protection




Klok, in prep

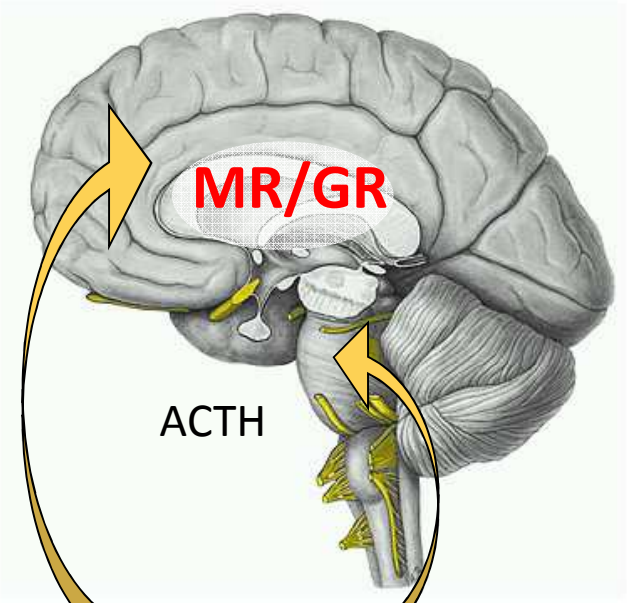
# Implications of human MR-gene variants on endophenotypes / depression

## Behavior

Optimism

Rumination

Depression




## Molecular Studies

Decreased activity MR

=

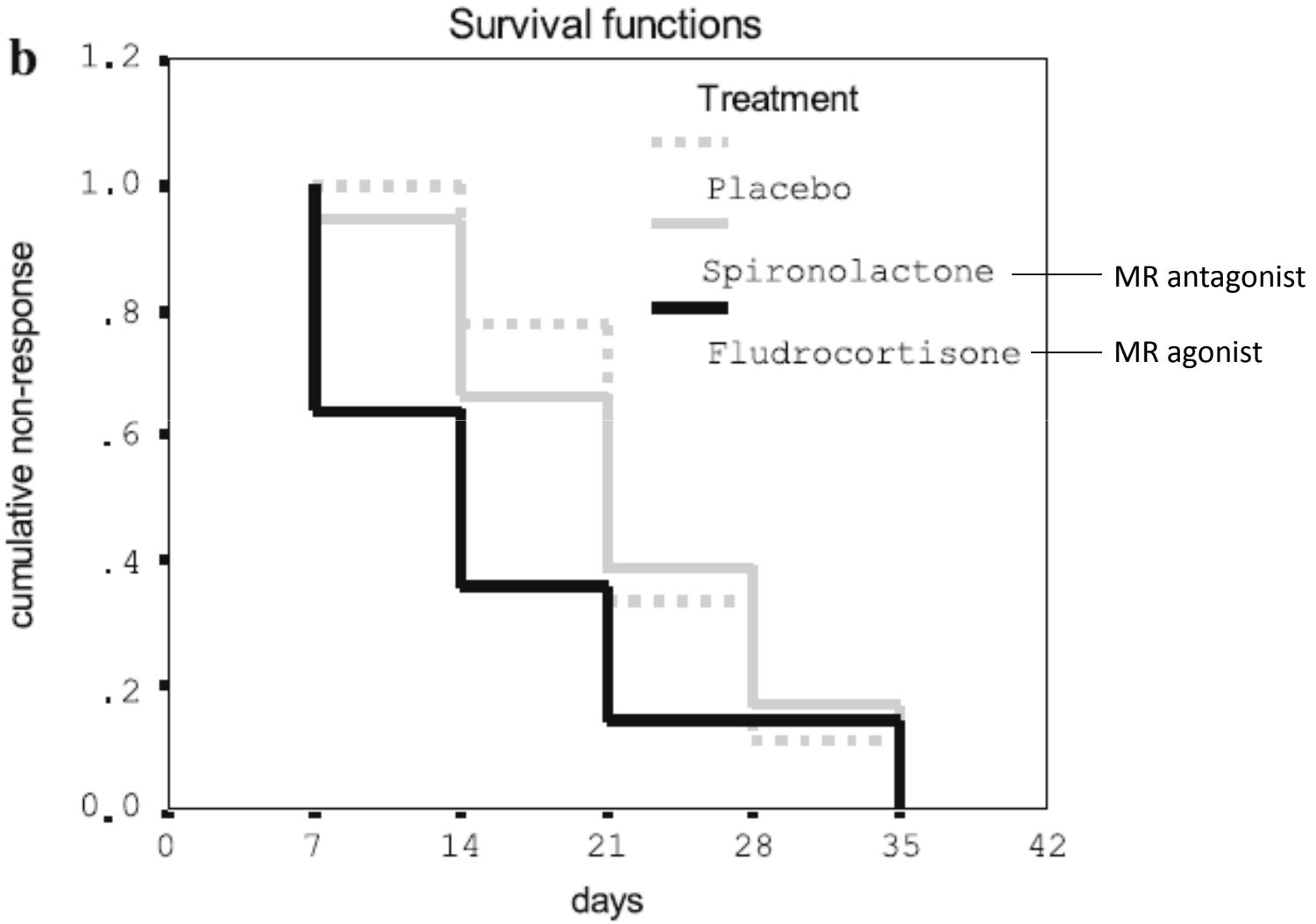
vulnerability factor

## Stress-response

## MR is a new drug target

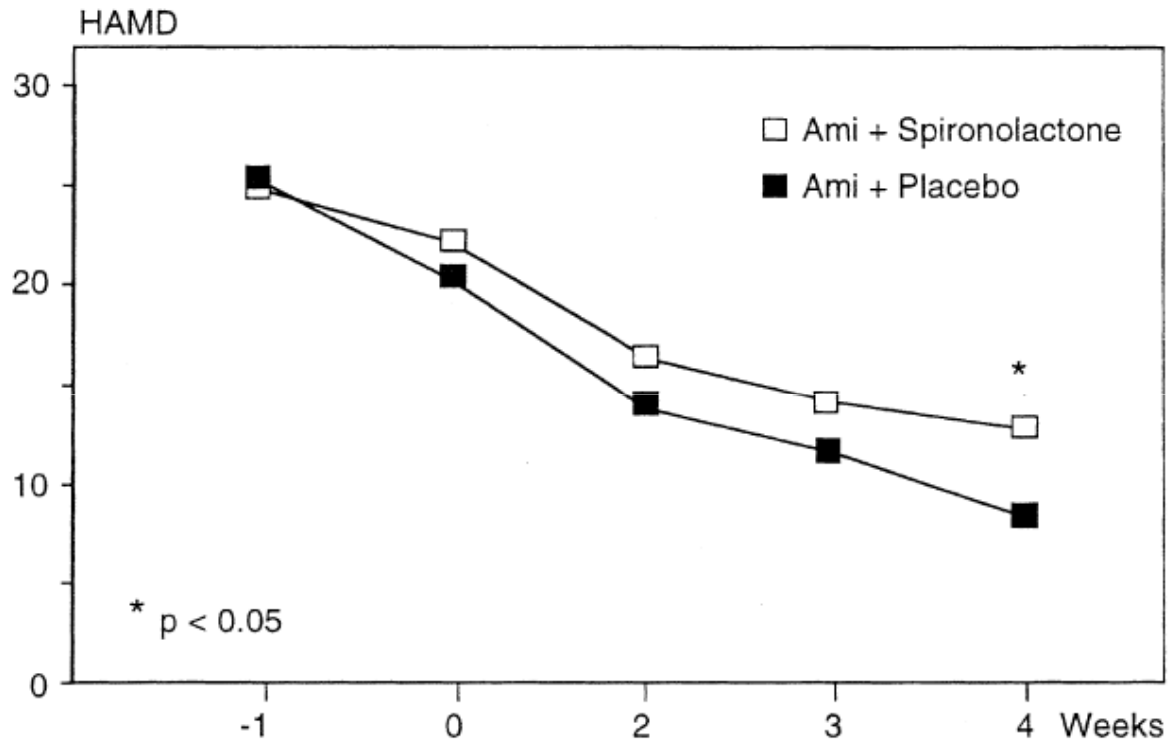
Stimulation improves handling stress

# Fludrocortisone improves treatment of depression




Otte et al; PNE '09

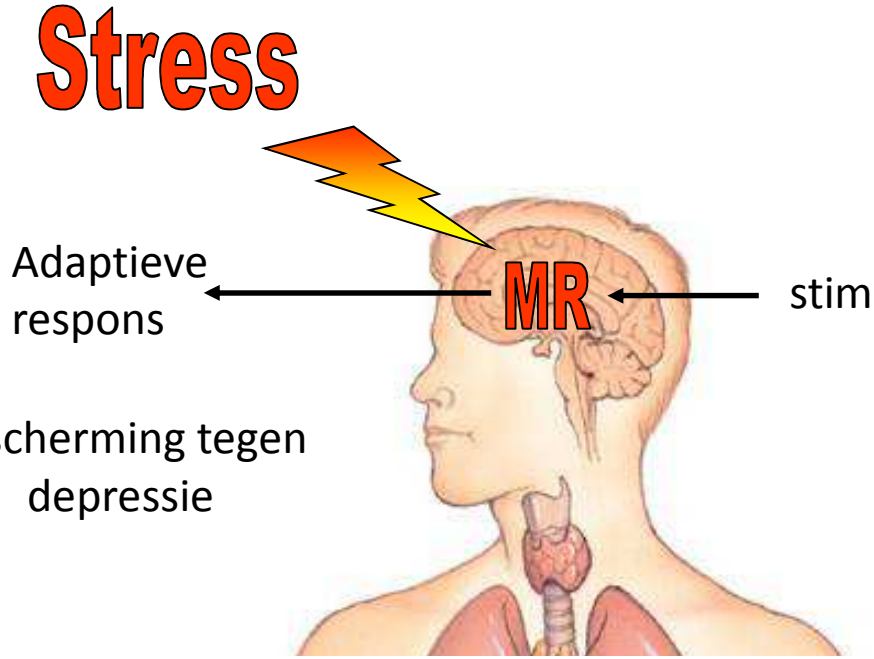
PATIENTS COTREATED WITH SPIRONOLACTONE FOR 10 DAYS RESPONDED LESS FAVORABLY TO AMITRIPTYLINE THAN PATIENTS COTREATED WITH PLACEBO




Holsboer et al, JPsyRes ’99

# MR als nieuwe behandeling van depressie

MR = cortisol / stress receptor




Adaptieve respons

stimulatie

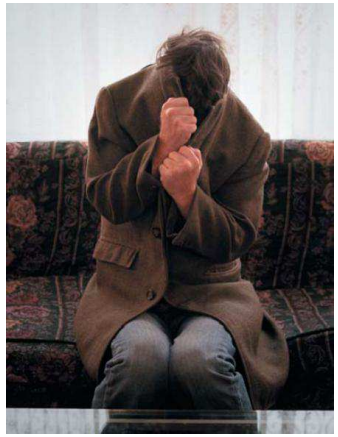
Bescherming tegen depressie

MR-modulatie
+
“klassieke antidepressiva”

**Personalized medicine: effect of functional genotypes**

| | Dose agonist | | |
|---|---|---|---|
| *MR-genotype* | low | middle | high |
| *1/1; 3/3;1/3* | | | **X** |
| *2/2* | **X** | | |
| *1/2; 2/3* | | **X** | |

# Nieuwe behandeling depressie: focus op stress-systeem



Selection of patients

Genotyping
Stress-measures
Others ?

MR-stimulation as add on to SSRI's or psychotherapy

Improved and faster recovery