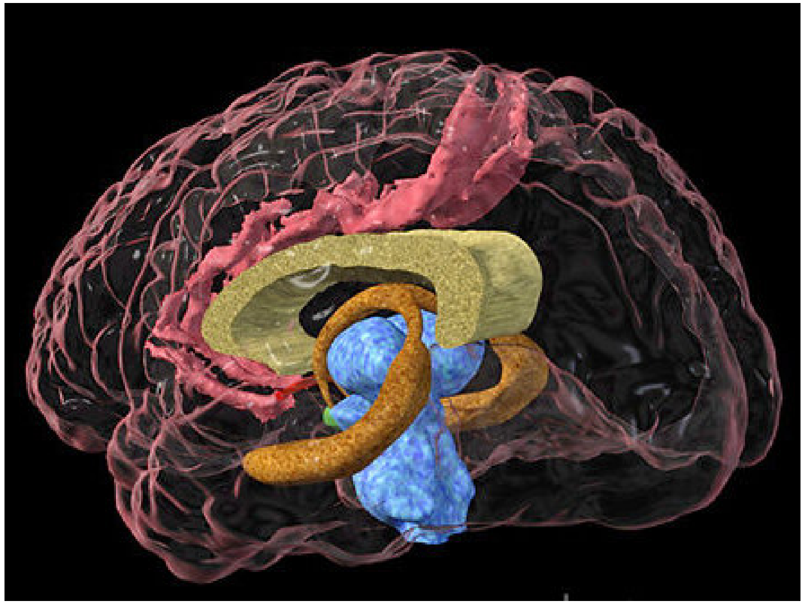
# Gebrochene Seele – gebrochenes Herz

## Warum Depressionen das Risiko von Herzinfarkt und Schlaganfall erhöhen

Klinikum Braunschweig



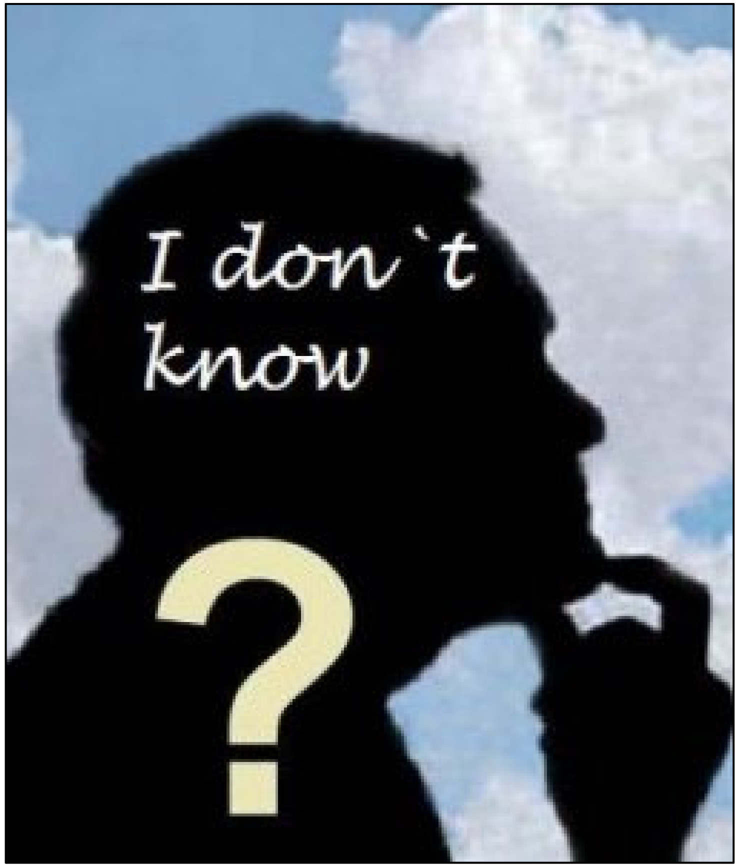
**Jan T. Kielstein**

**Medizinische Klinik V | Nephrologie und Hypertensiologie**

**Städtisches Klinikum Braunschweig**

# "Unter allen Leidenschaften der Seele bringt die Trauer am meisten Schaden für den Leib. „

(Thomas von Aquin)



1) Ist das Problem häufig?

2) Die Zusammenhänge

3) Was sollte ich tun?

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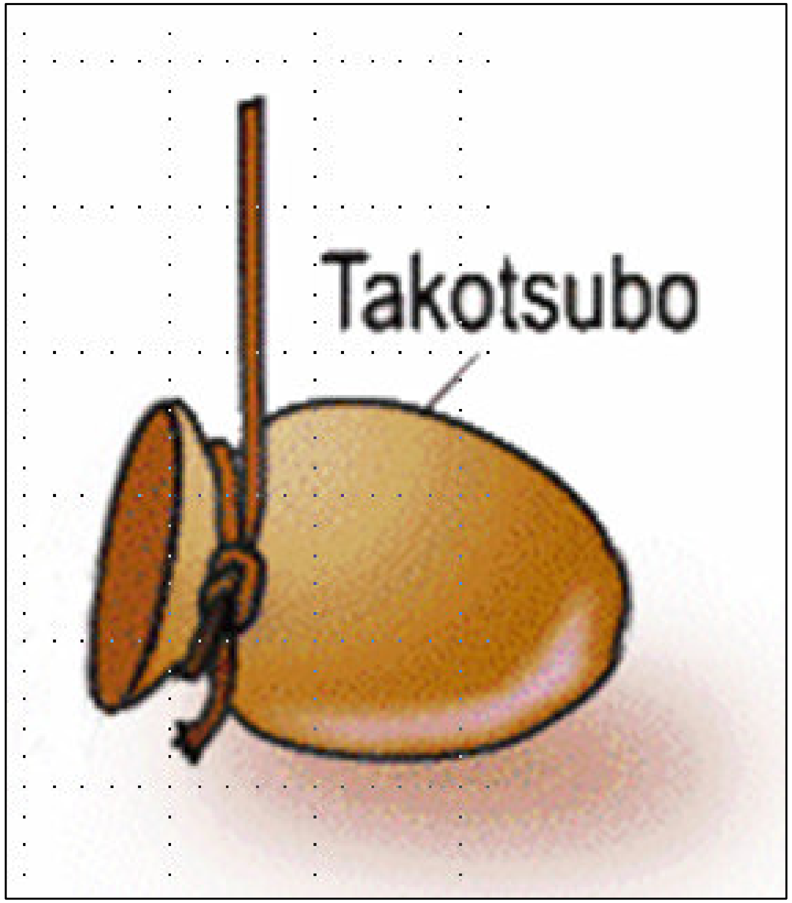


**1) Ist das Problem häufig?**

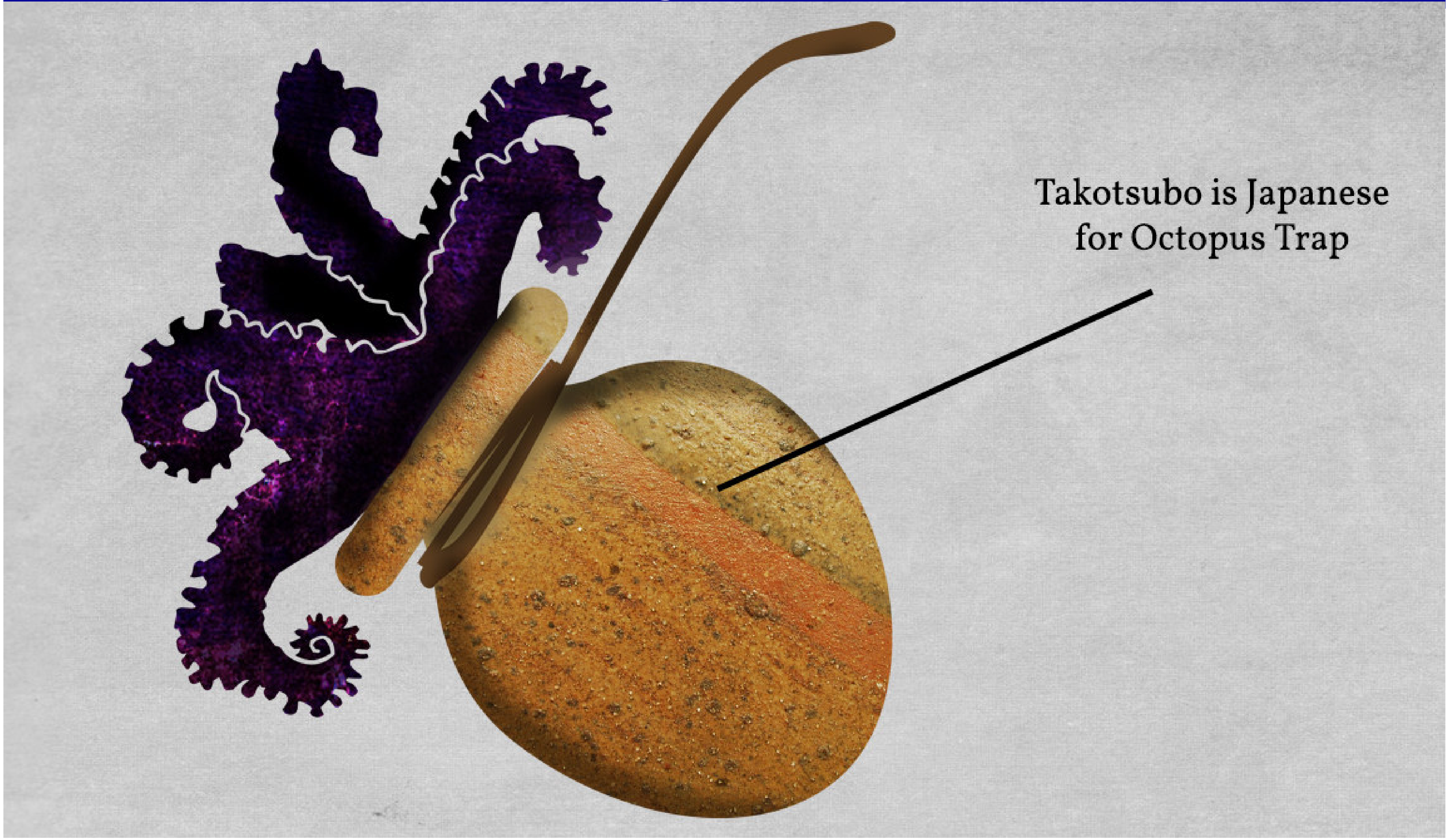
2) Die Zusammenhänge

3) Was sollte ich tun?

Klinikum Braunschweig

# Die Tako-Tsubo-Kardiomyopathie
# Syndrom des »gebrochenen Herzens«

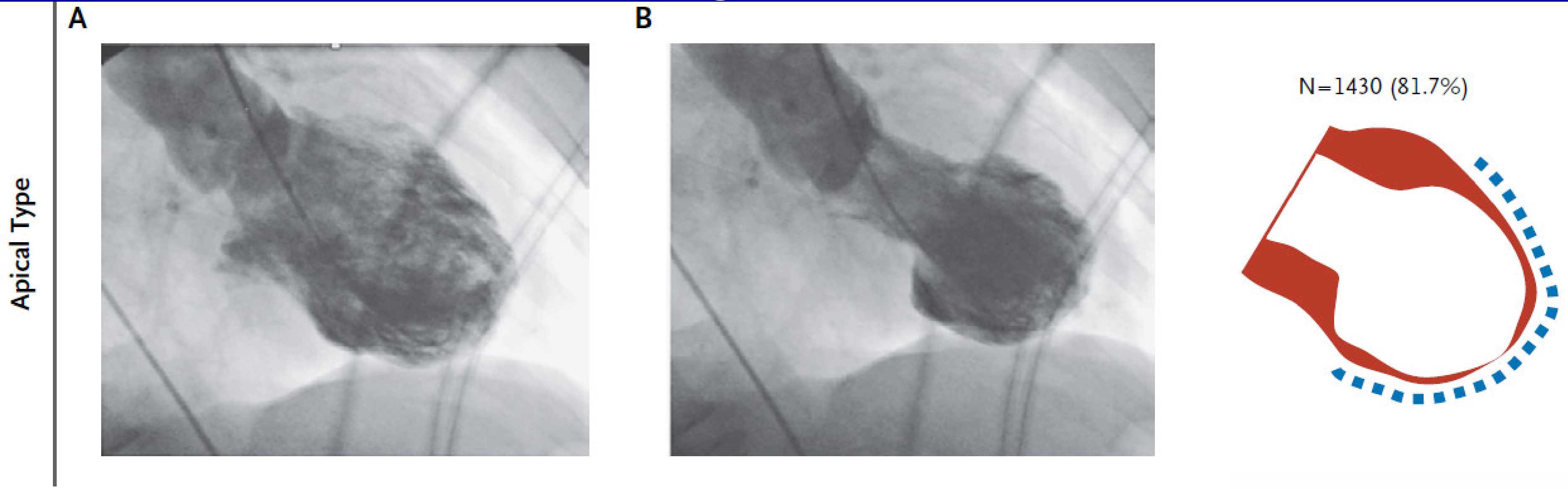
TEMPLIN et al. *N Engl J Med* 373(10):929-38, 2015

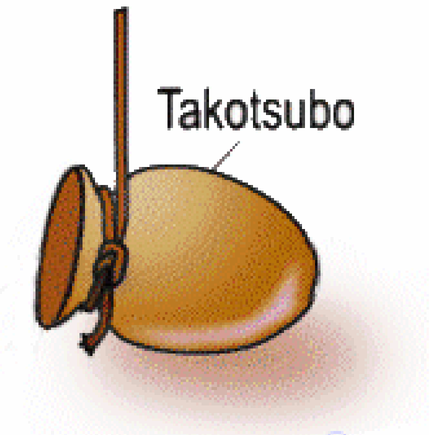


Takotsubo is Japanese
for Octopus Trap

# Die Tako-Tsubo-Kardiomyopathie
## Syndrom des »gebrochenen Herzens«

**TEMPLIN et al. *N Engl J Med* 373(10):929-38, 2015**

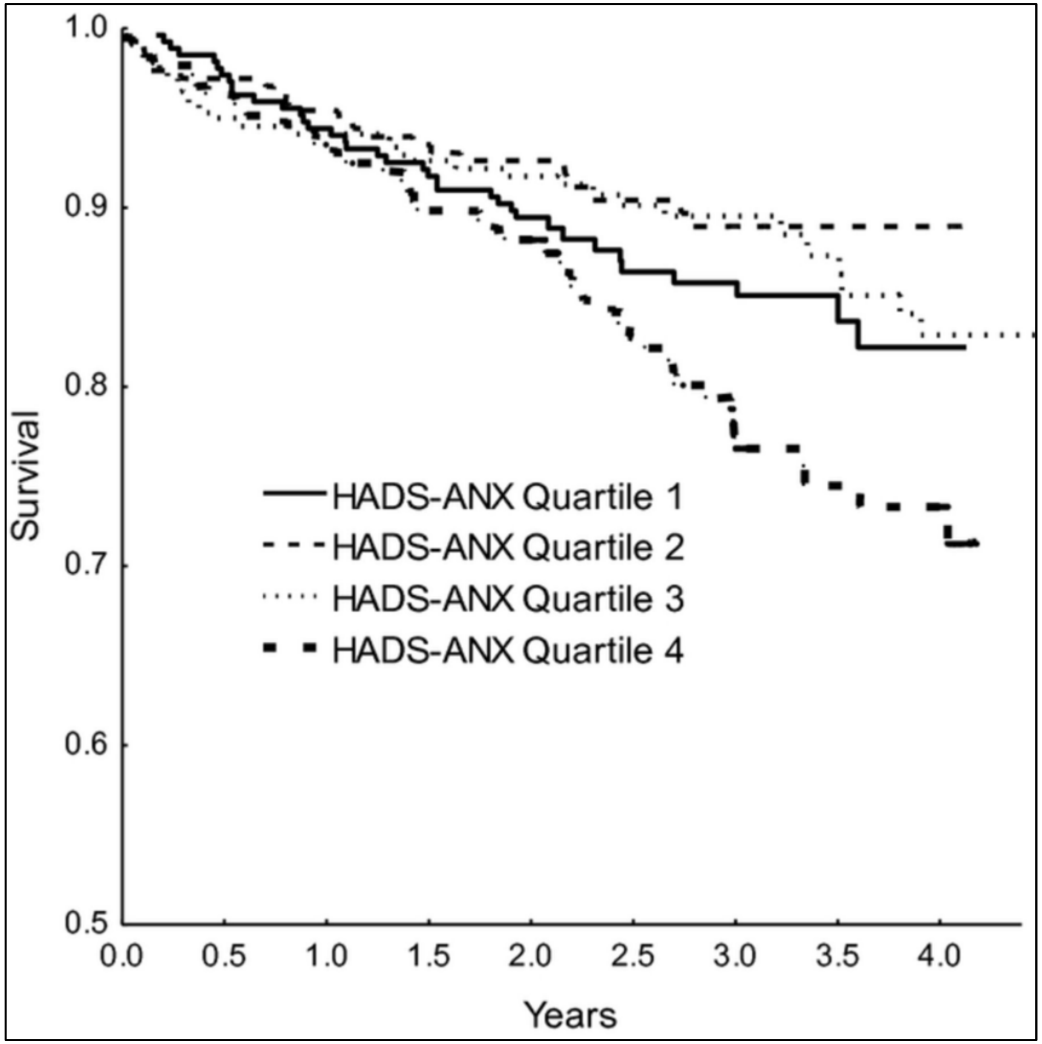

A
B
Apical Type
N=1430 (81.7%)



Striped Giraffe Press © 2005

# Angst, Depression und Sterblichkeit von Patienten mit Koronarer Herzkrankheit

WATKINS et al. *J Am Heart Assoc* 19;2(2):e000068, 2013



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# Häufigkeit der Depression bei körerlichen Erkrankungen

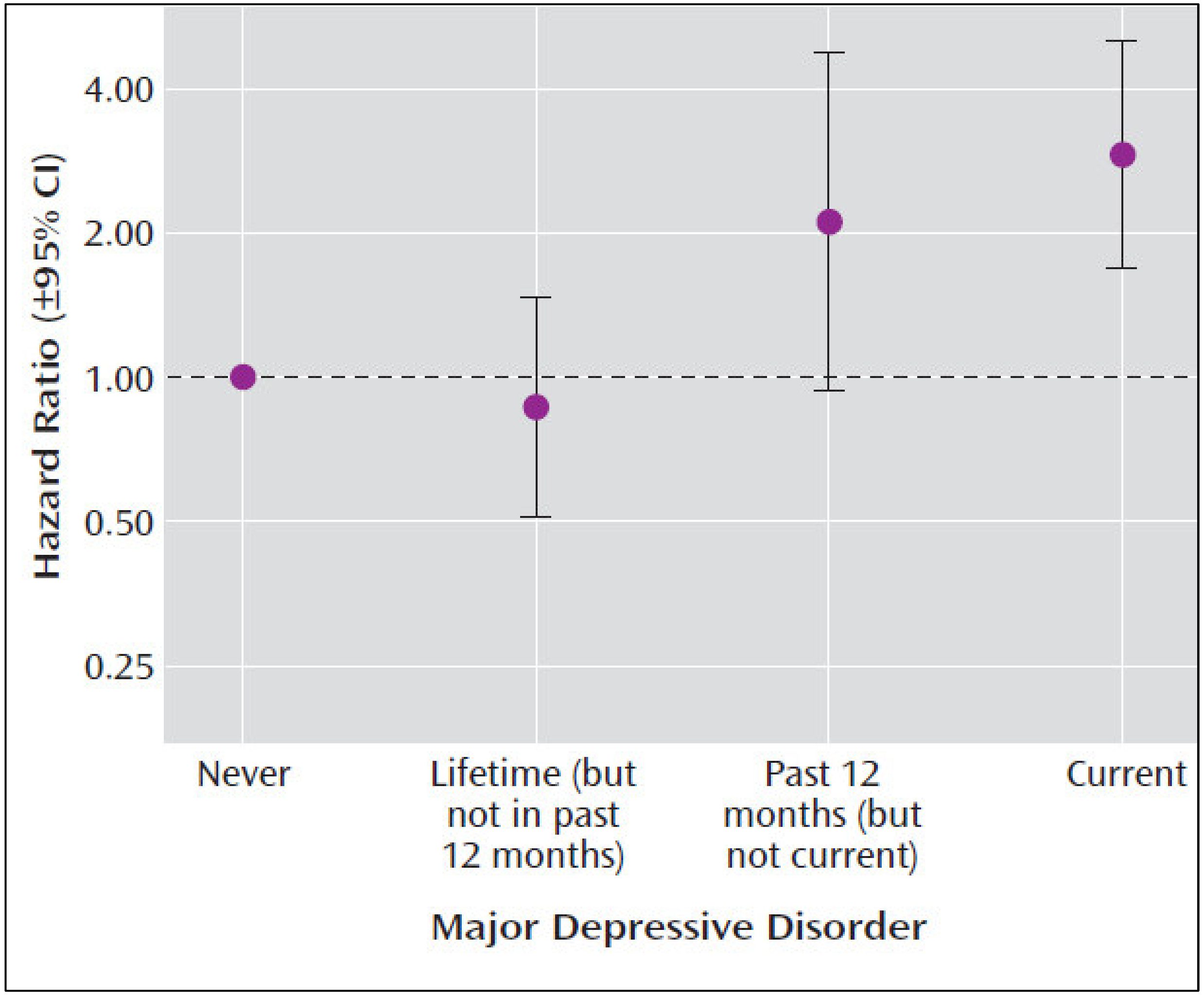
Rundell JR, Wise MG (Eds). Textbook of Consultation-Liaison Psychiatry.
American Psychiatric Press, Washington, D.C., 1996

| Erkrankung | Prävalenz (%) |
|---|---|
| Krebs | 20-38 |
| Chronic fatigue Syndrom | 17-46 |
| Chronische Schmerzen | 21-32 |
| Koronare Herzerkrankung | 16-19 |
| Cushing- Syndrom | 67 |
| Demenz | 11-40 |
| Diabetes mellitus | 24 |
| Epilepsie | 55 |
| Haemodialyse | 6.5 |
| HIV Infektion | 30 |
| Chorea Huntington | 41 |
| Hyperthyreose | 31 |
| Multiple Sklerose | 6-57 |
| Morbus Parkinson | 28-51 |
| Schlaganfall | 46 |

# Depression und koronare Herzkrankheit

(8261 Männer und 11388 Frauen | Alter 41–80 Jahre | Nachbeobachtung 8,5 Jahre)

SURTEES et al. *Am J Psychiatry* 165:515–523, 2008



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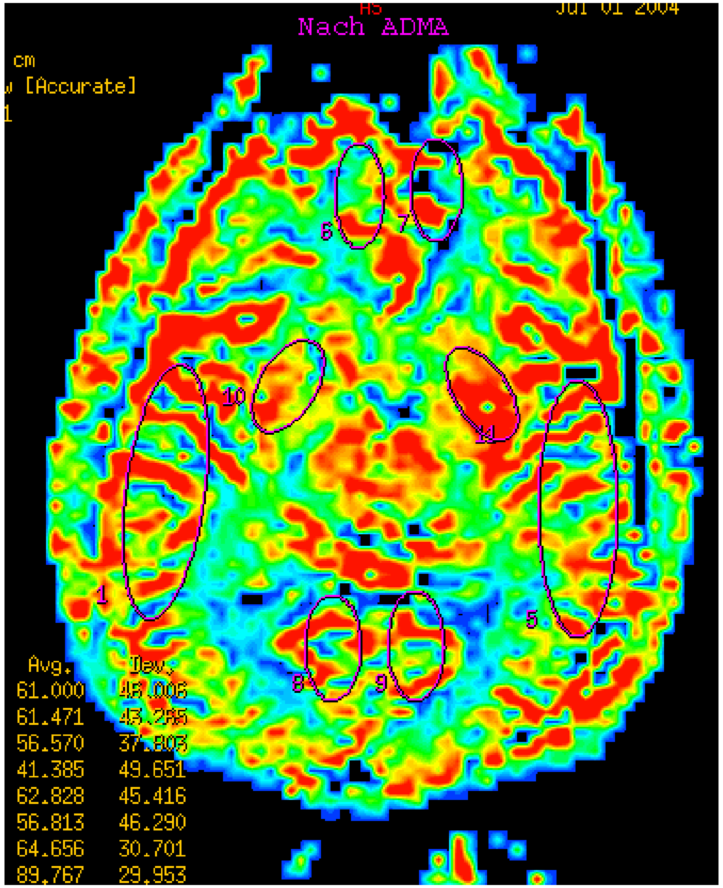
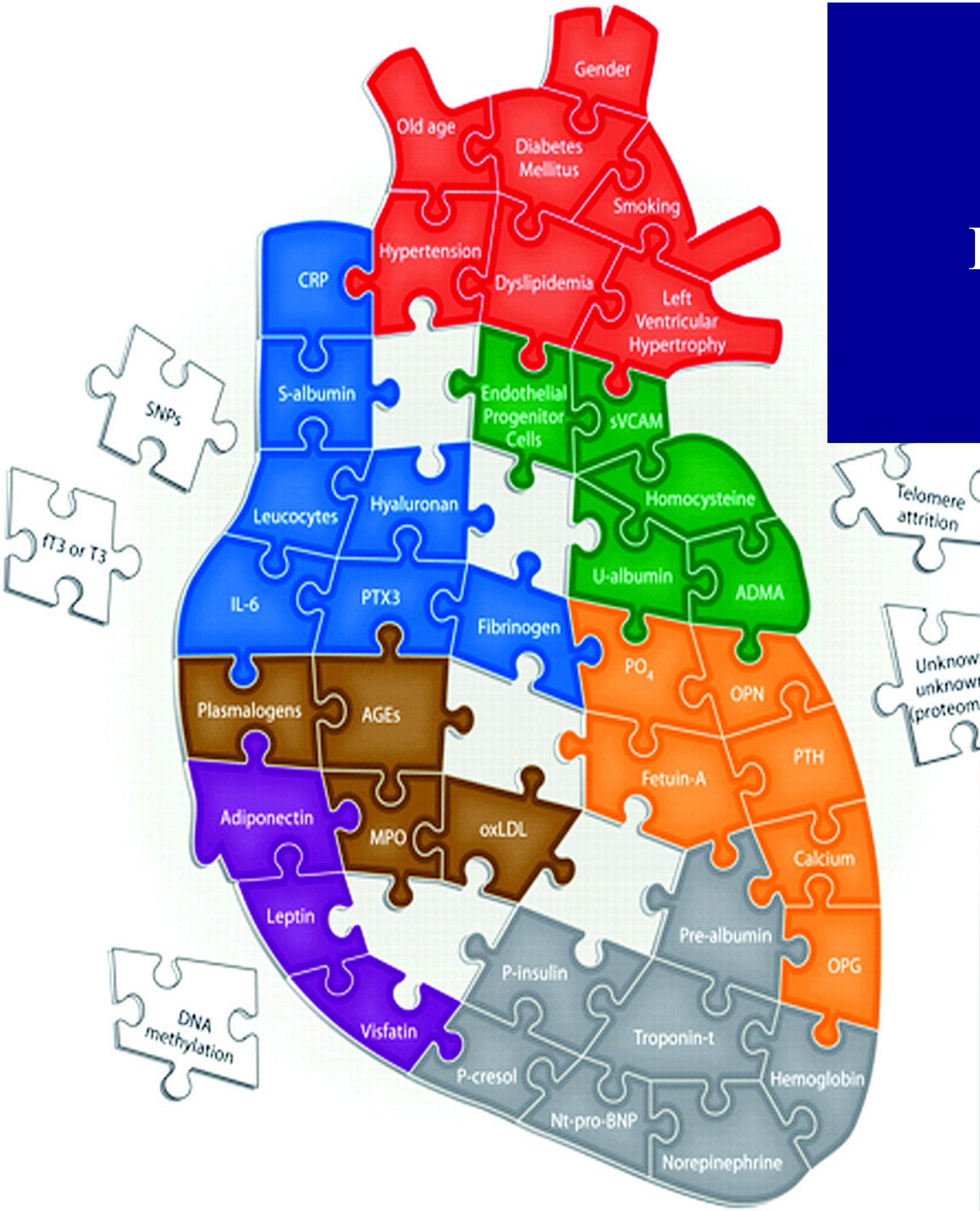

HS
Jul 01 2004
Nach ADMA
cm
[Accurate]
1
2
3
4
5
6
7
8
9
10
11
Avg. Dev.
61.000 48.006
61.471 43.255
56.570 37.803
41.385 49.651
62.828 45.416
56.813 46.290
64.656 30.701
89.767 29.953

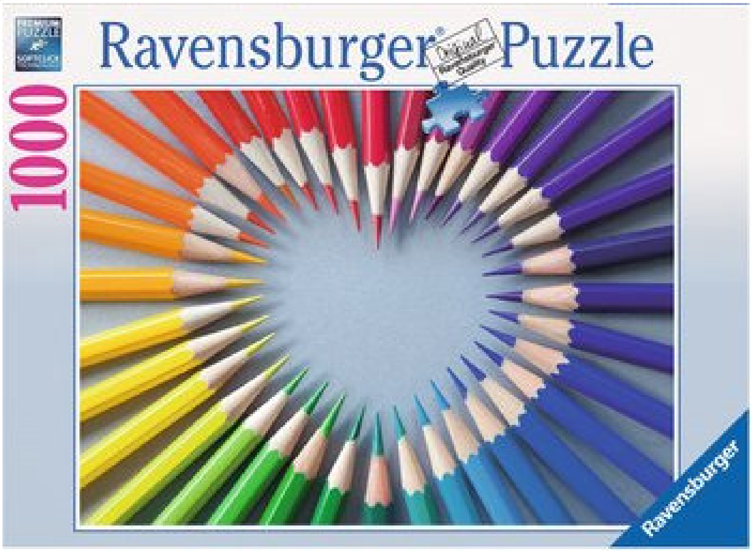
1) Ist das Problem häufig?

**2) Die Zusammenhänge**

3) Was sollte ich tun?

# Depression und Herzerkrankung – Ein Puzzle mit 1000 Teilen


Gender
Old age
Diabetes Mellitus
Smoking
Hypertension
Dyslipidemia
Left Ventricular Hypertrophy
CRP
S-albumin
Endothelial Progenitor Cells
sVCAM
SNPs
fT3 or T3
Leucocytes
Hyaluronan
Homocysteine
Telomere attrition
IL-6
PTX3
Fibrinogen
U-albumin
ADMA
PO$_4$
OPN
Unknown unknowns (proteomics)
Plasmalogens
AGEs
Fetuin-A
PTH
Adiponectin
MPO
oxLDL
Calcium
Leptin
Pre-albumin
P-insulin
OPG
DNA methylation
Visfatin
Troponin-t
P-cresol
Hemoglobin
Nt-pro-BNP
Norepinephrine

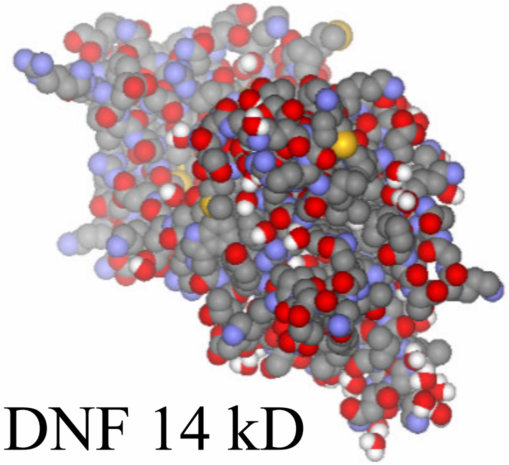

Ravensburger Puzzle
Original Ravensburger Quality
1000
Ravensburger

# Welche Stoffe sind im Blut von depressiven Patienten erhöht ?

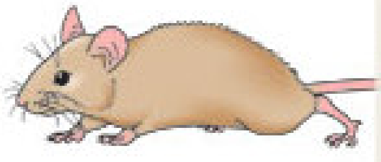
Selley et al. J Affect Disord. 2004
McEvoy et al. J Affect Disord. 2013
Barani et al. Psychosom Med. 2014

# The molecular neurobiology of depression

## KRISHNAN& NESTLER Nature 455, 894-902, 2008



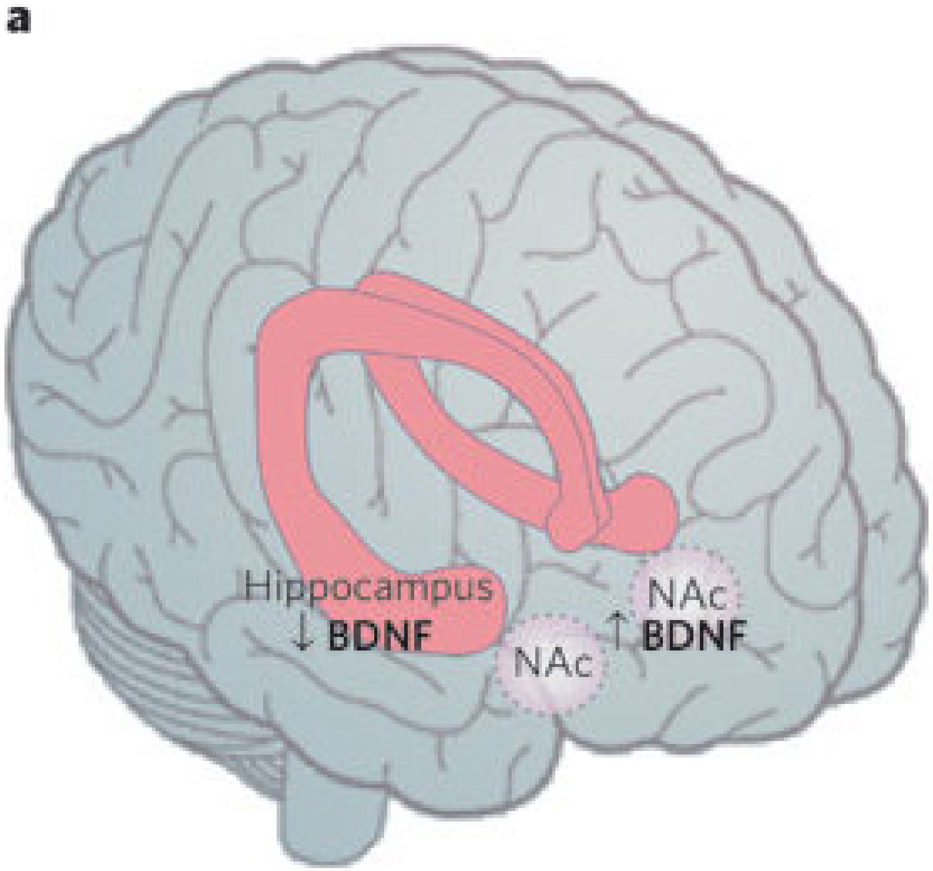
BDNF 14 kD



BDNF Met 66/Met 66

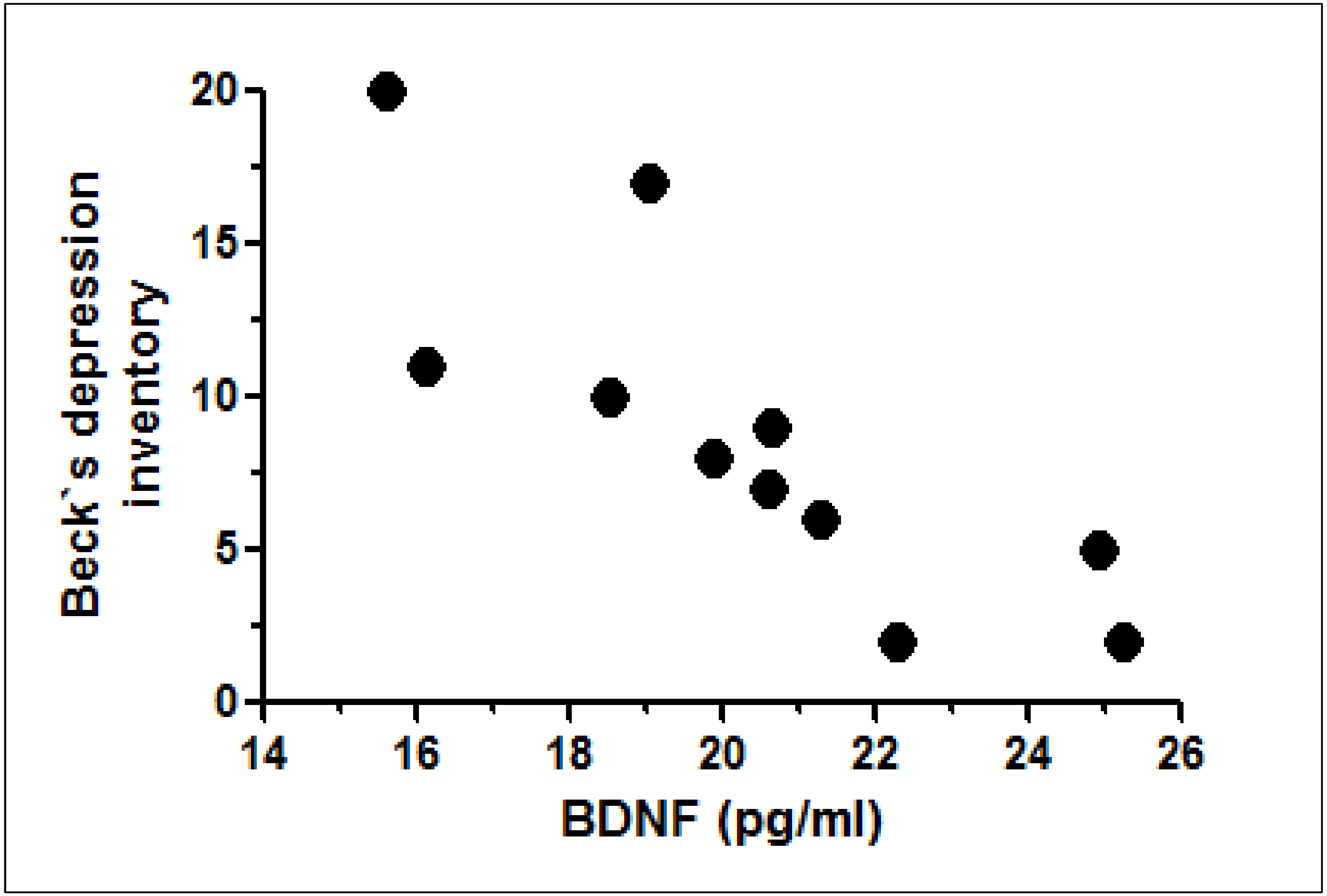
**Behavioural responses compared with wild-type mice (BDNF Val 66/Val 66)**

- Equivalent response in forced swim test
- Increased anxiety-like behaviour
- Increased resilience to social defeat

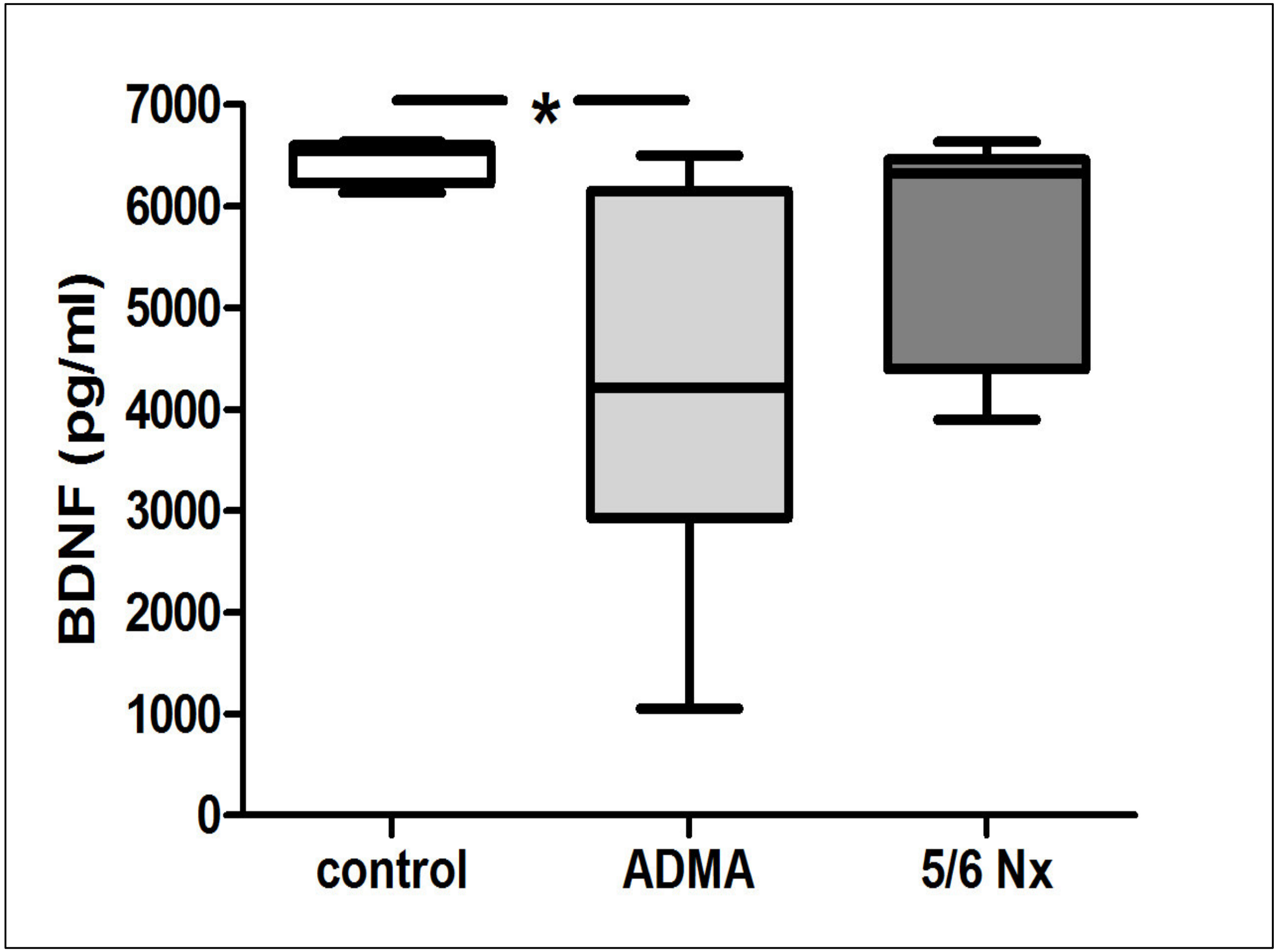


# Der Blutmarker BDNF und der Depressionstest Beck Depression Inventory (BDI)

KIELSTEIN *Nephrol Dial Transplant*. 1699-705, 2015



# Effect of ADMA infusion and 5/6 nephrectomy on BDNF levels

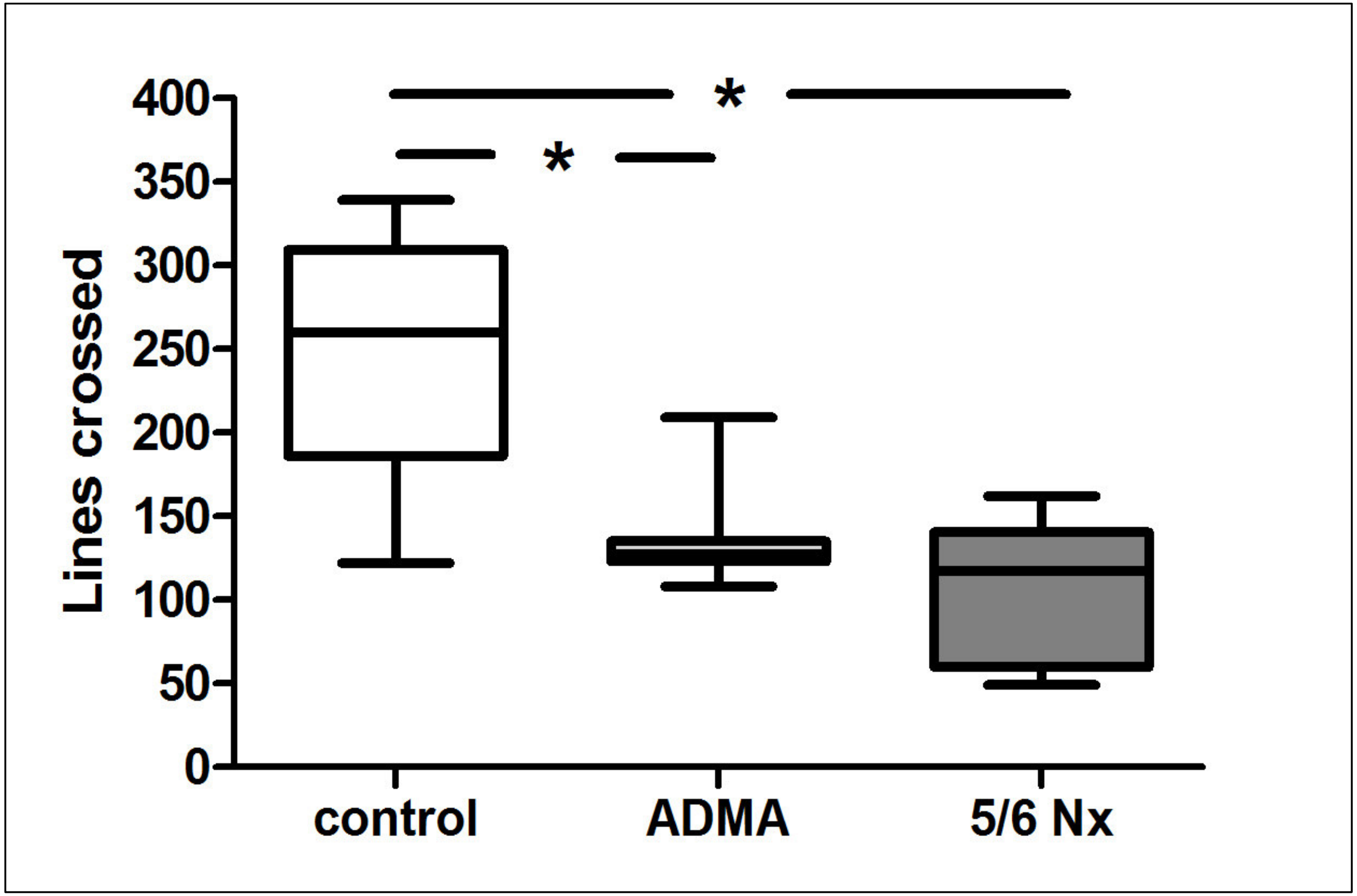


Klinikum Braunschweig

# Bewegung

# Bewegung

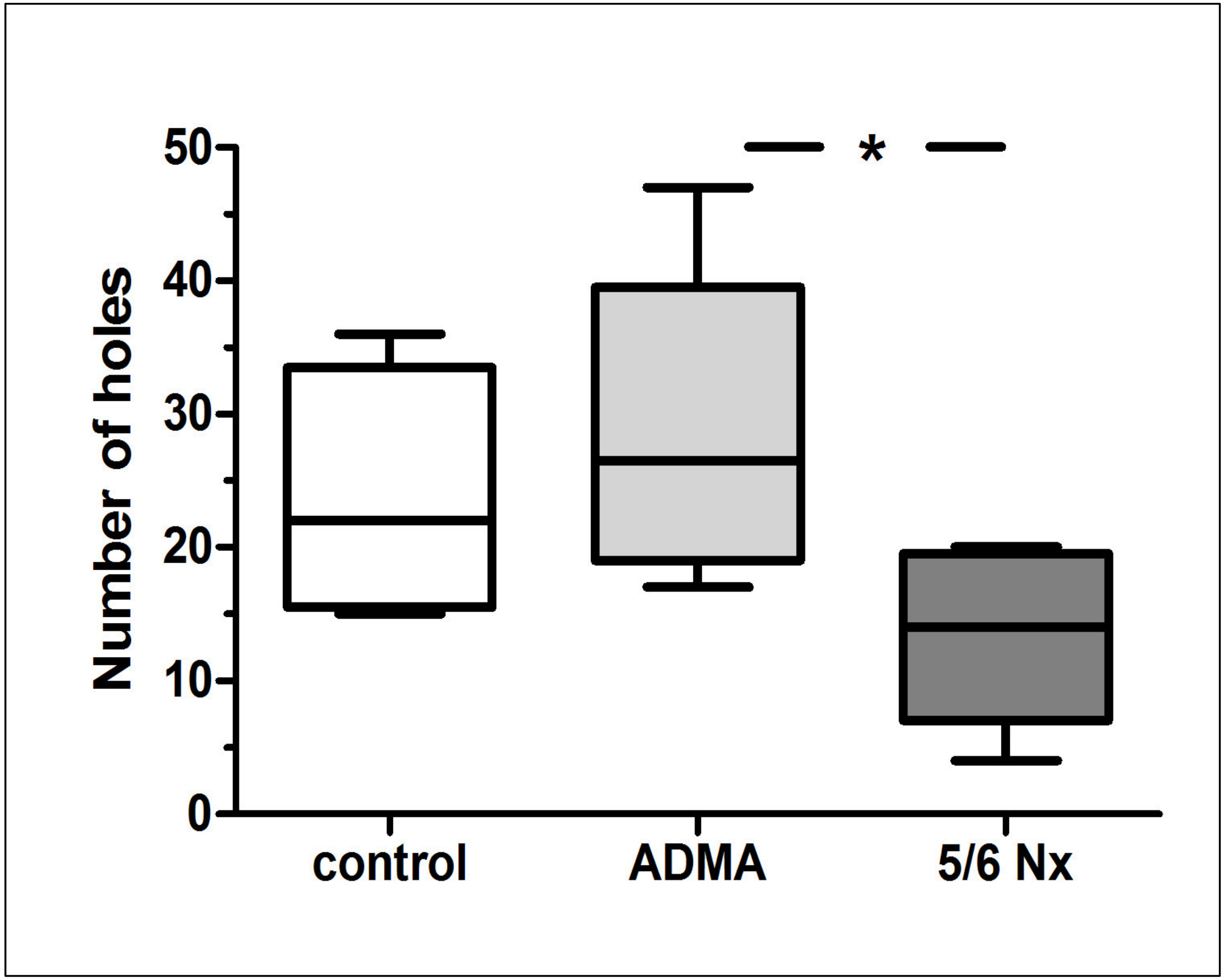
## Lines crossed

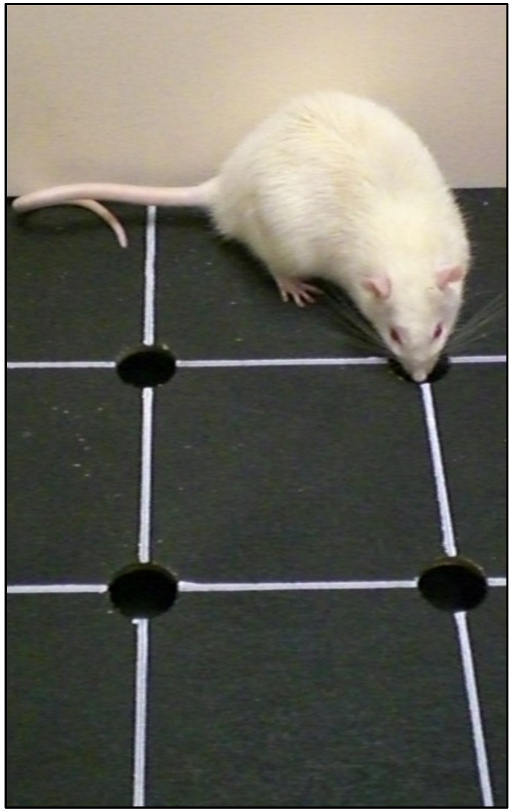


Klinikum Braunschweig

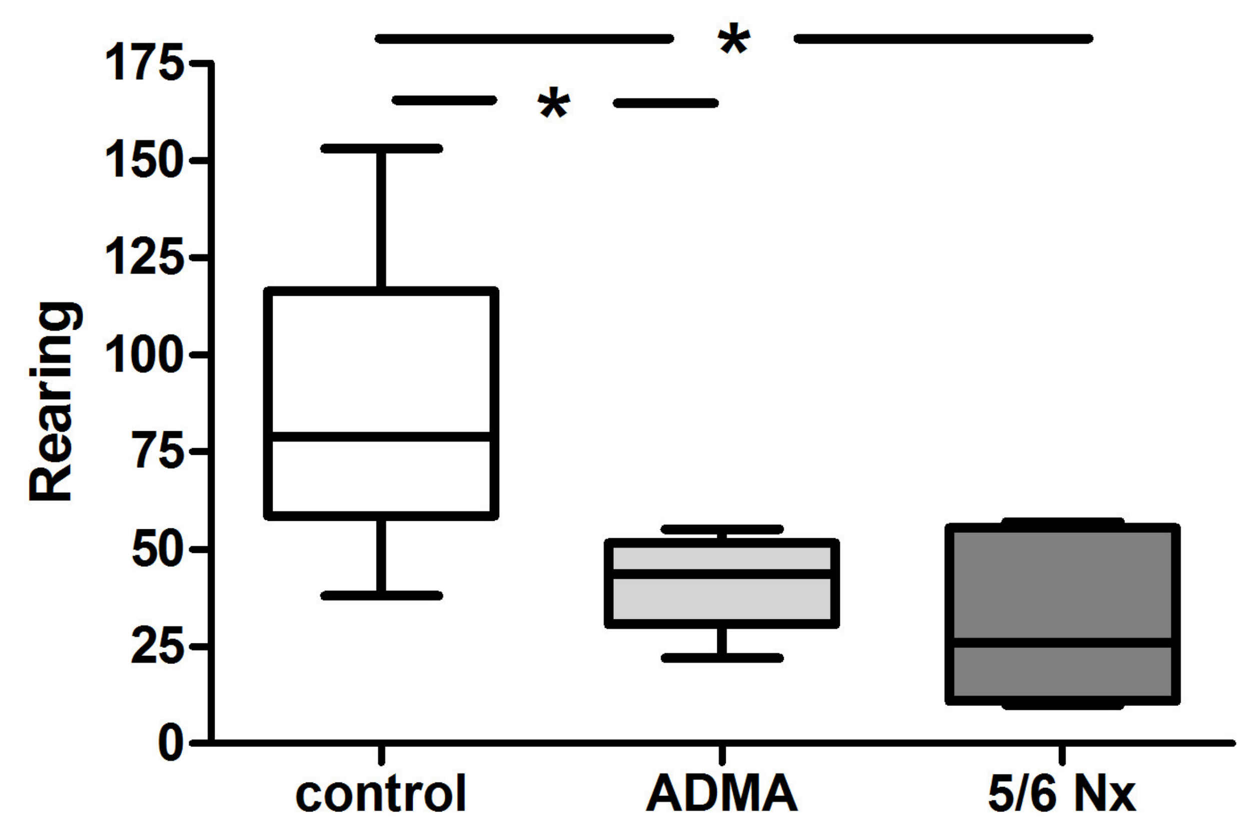
Neugier

# Neugier-Test





# Neugier-Test



Klinikum
Braunschweig

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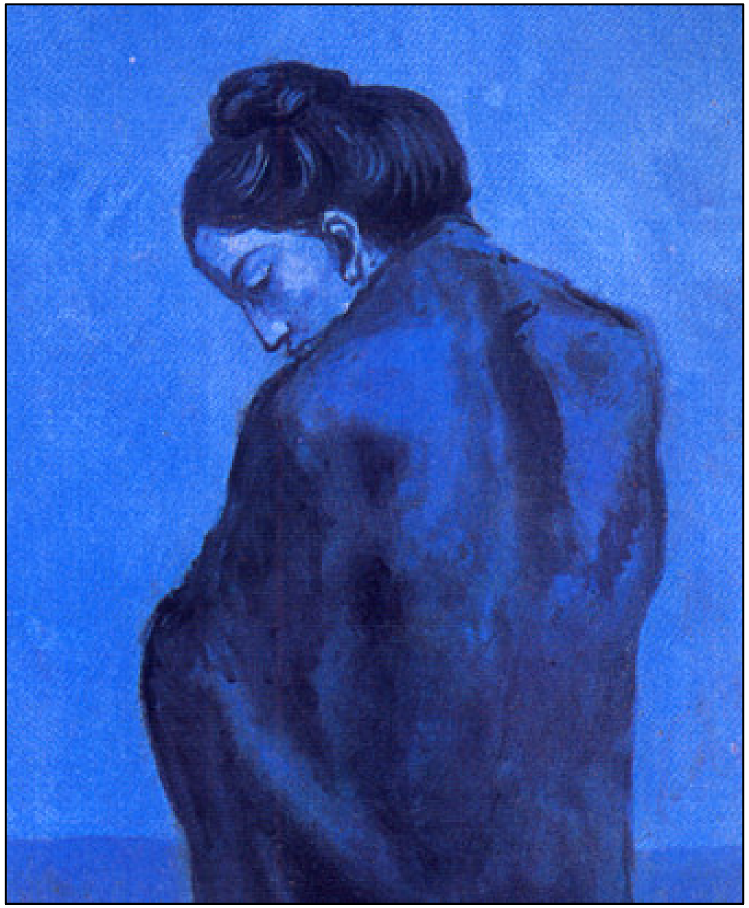


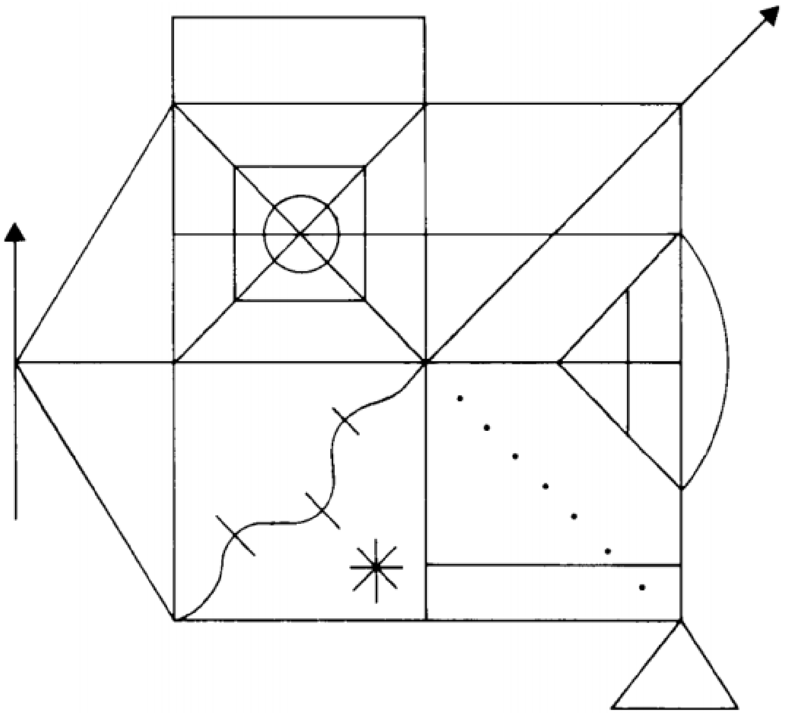
1) Ist das Problem häufig?

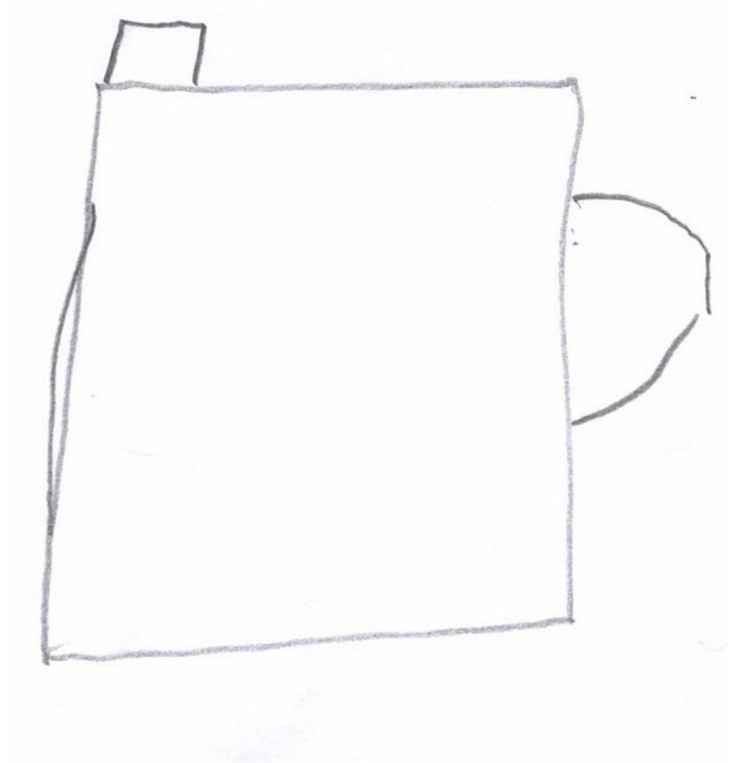
2) Die Zusammenhänge

**3) Was sollte ich tun?**

# Die körperliche Erkrankung muss behandelt werden!

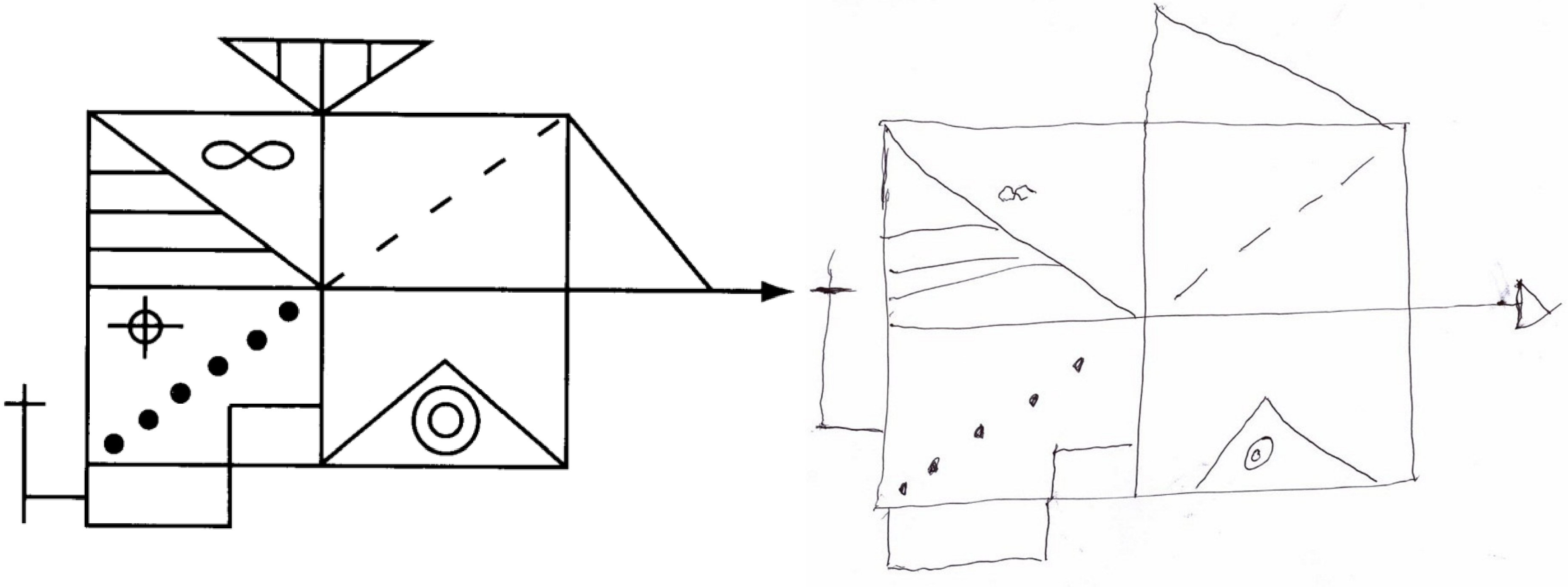
SCHNEIDER et al. *BMC Nephrol* 13:86, 2012





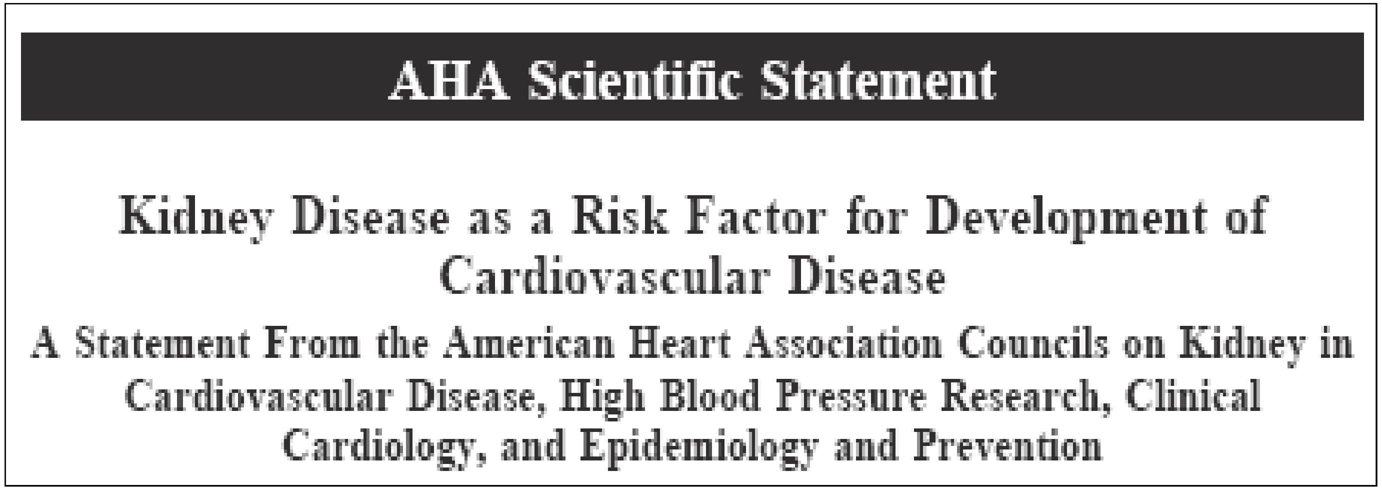
# Die körperliche Erkrankung muss behandelt werden!

SCHNEIDER et al. *BMC Nephrol BMC Nephrol* 13:86, 2012



# Kardiovskuläre Risikofaktoren müssen behandelt werden

**SARNAK et al. *Circulation* 108: 2154-2169, 2003**

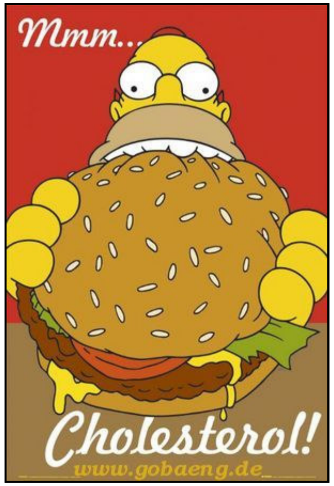


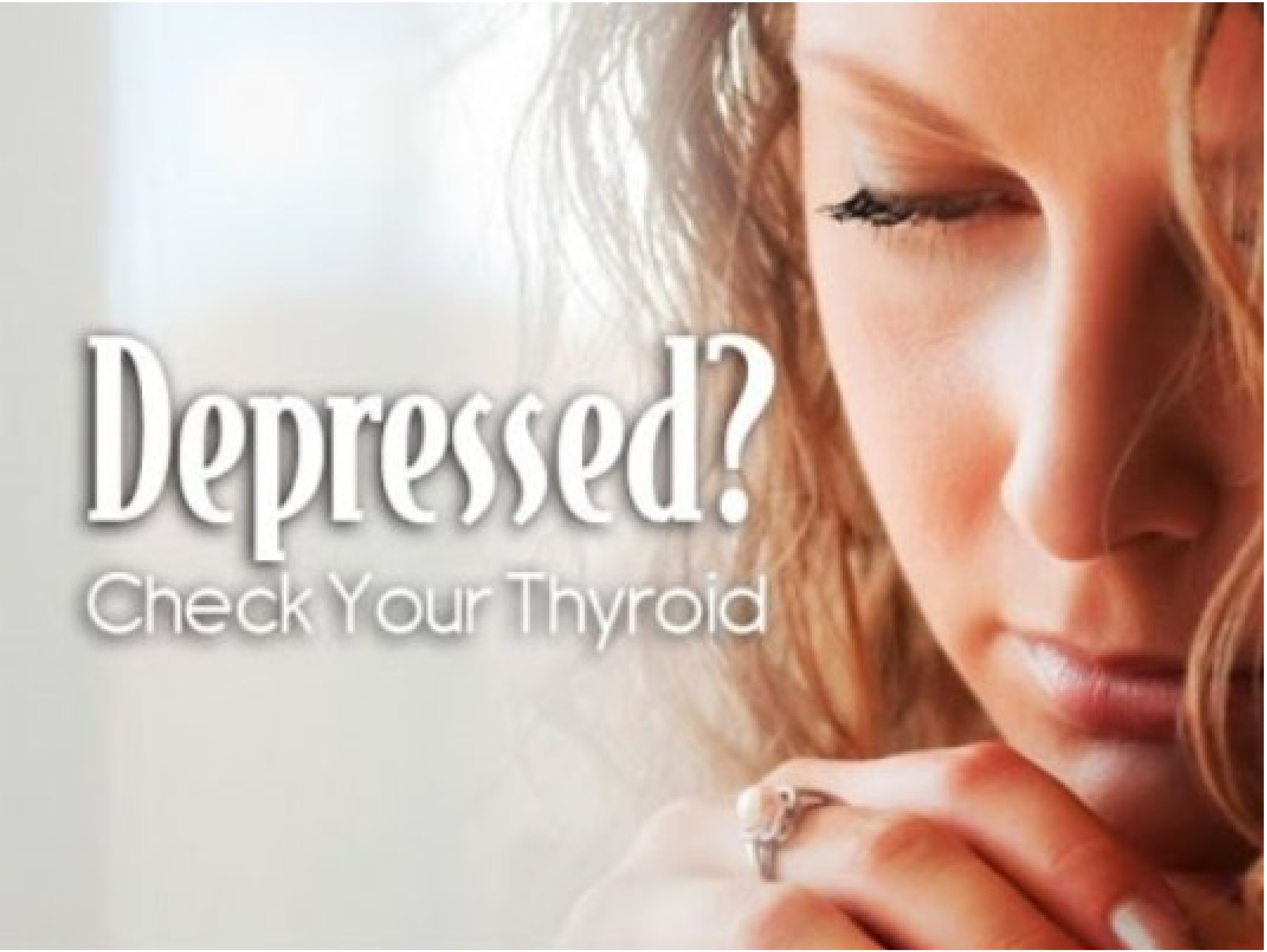
AHA Scientific Statement

Kidney Disease as a Risk Factor for Development of Cardiovascular Disease

A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention

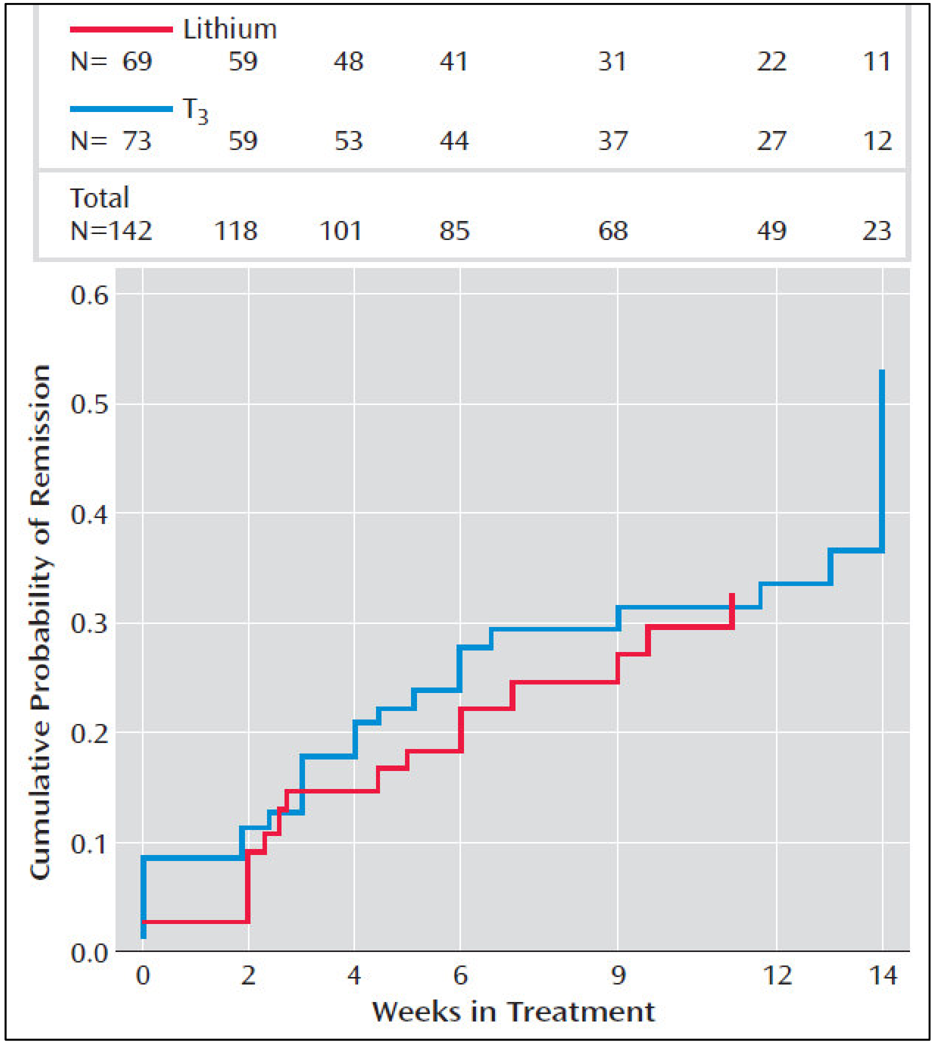
ACCUTREND Sensor
14:20
97
mg/dL
Diabetes


Mmm...
Cholesterol!
www.gobaeng.de


Depressed?
Check Your Thyroid

# A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report

**NIERENBERG et al.** *Am J Psychiatry.* **163(9):1519-30, 2006**



http://blog.besserhaushalten.de/wp-content/uploads/2013/01/Pillen.jpg

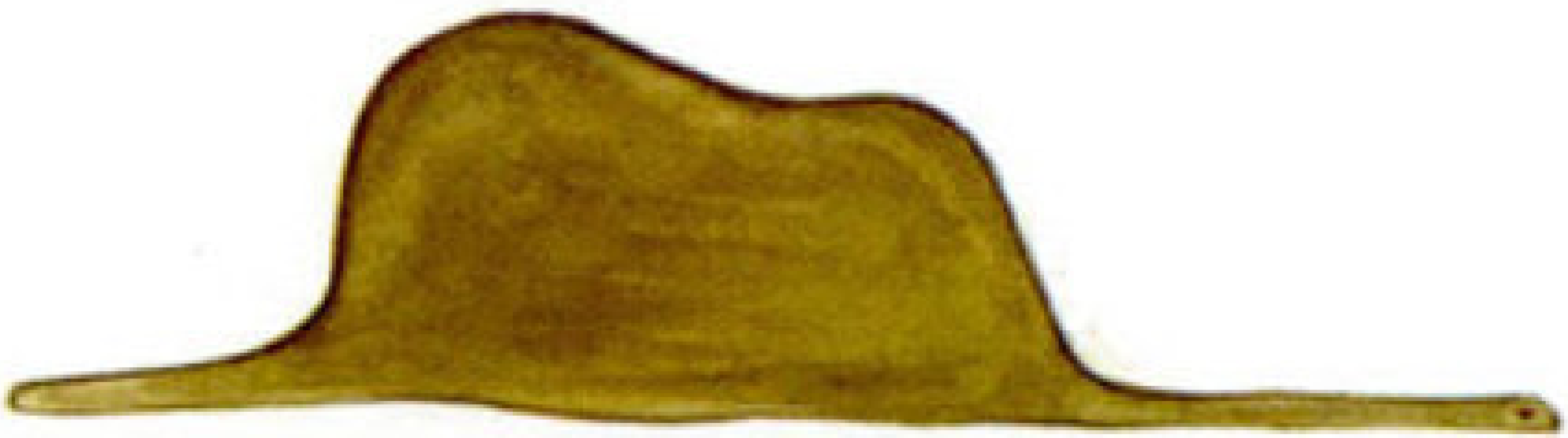
# Effect of Escitalopram on All-Cause Mortality and Hospitalization in Patients With Heart Failure and Depression: The MOOD-HF Randomized Clinical Trial.

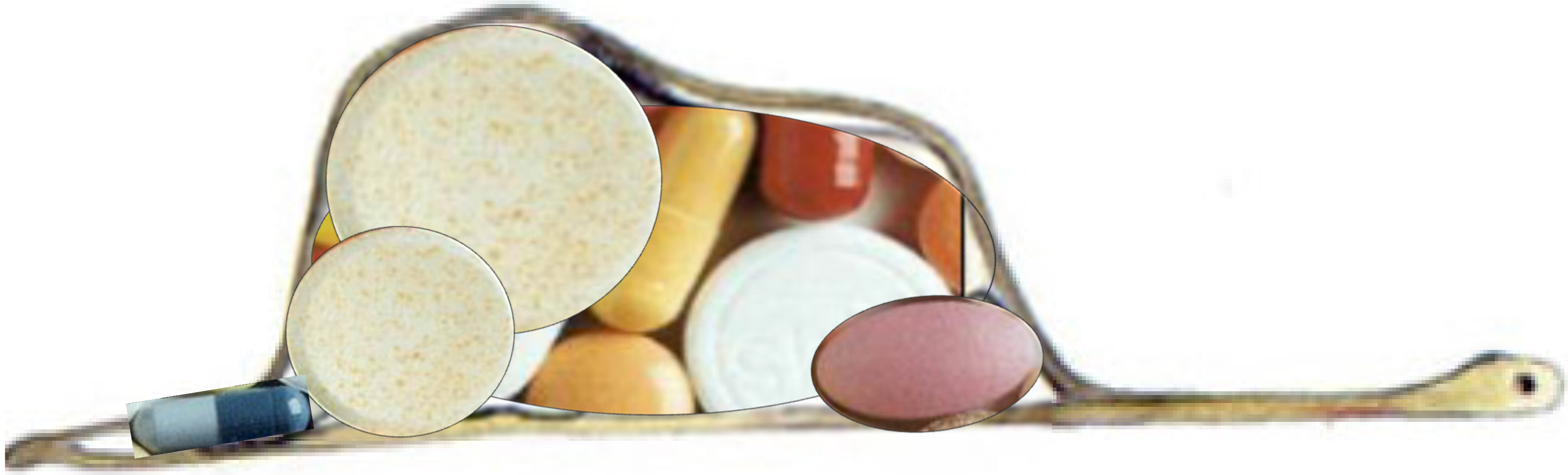
ANGERMANN et al. *JAMA* 28;315(24):2683-93, 2016

**Zusammenfassung:** Eine 18-monatige Therapie mit Citalopram reduziert bei Patienten mit Herzinsuffizienz weder die Sterblichkeit, noch die Häufigkeit von Krankenhausaufenthalten. Eine (alleinige) Therapie mit Escitalopram kann daher nicht empfohlen werden.

**“Perfektion ist nicht dann erreicht, wenn es nichts mehr hinzu zu fügen gibt, sondern wenn man nichts mehr weglassen kann.”**

Antoine de Saint-Exupéry

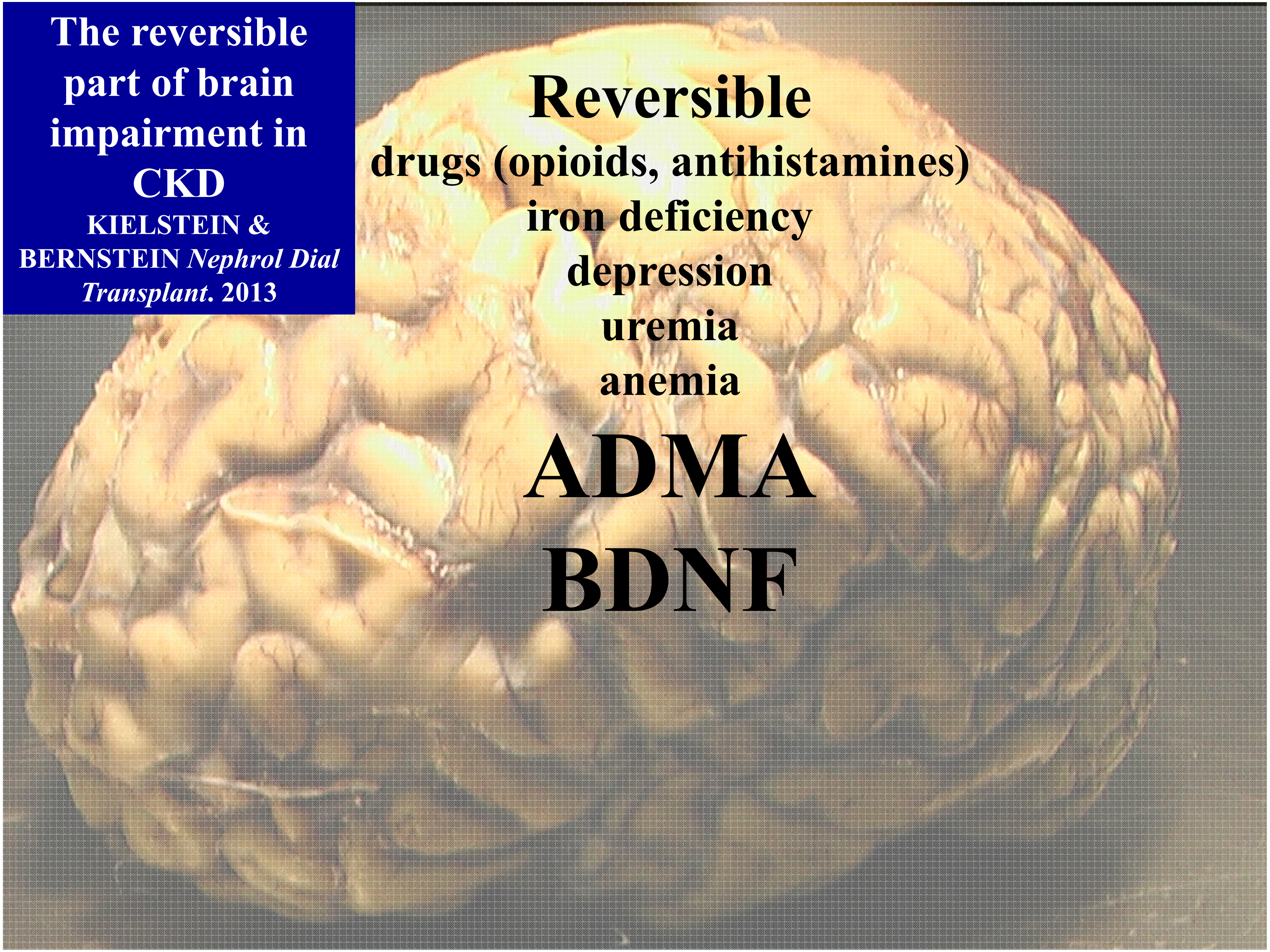




# I will survive

# The reversible part of brain impairment in CKD

KIELSTEIN & BERNSTEIN *Nephrol Dial Transplant.* 2013



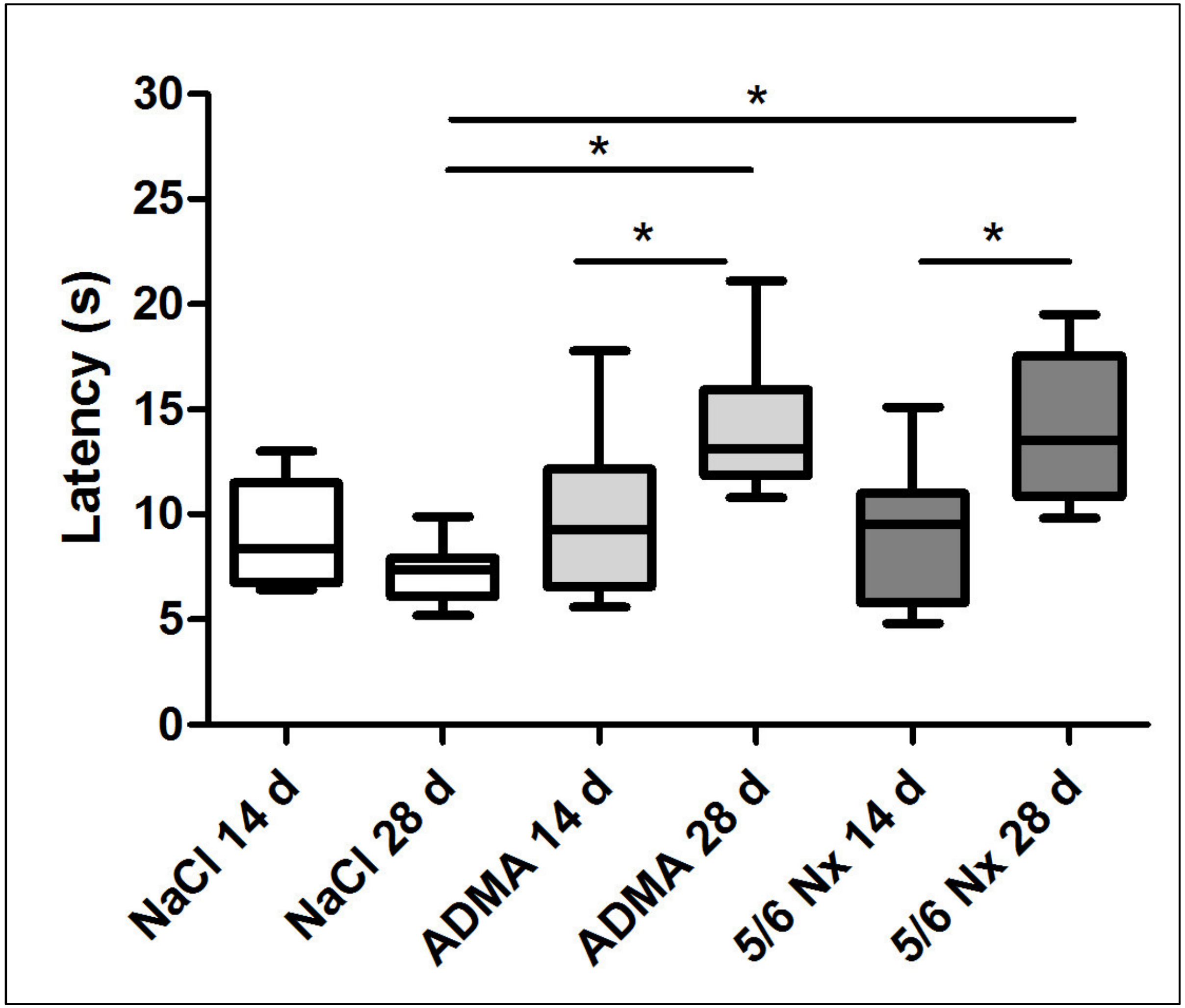
## Reversible

drugs (opioids, antihistamines)
iron deficiency
depression
uremia
anemia

**ADMA**
**BDNF**

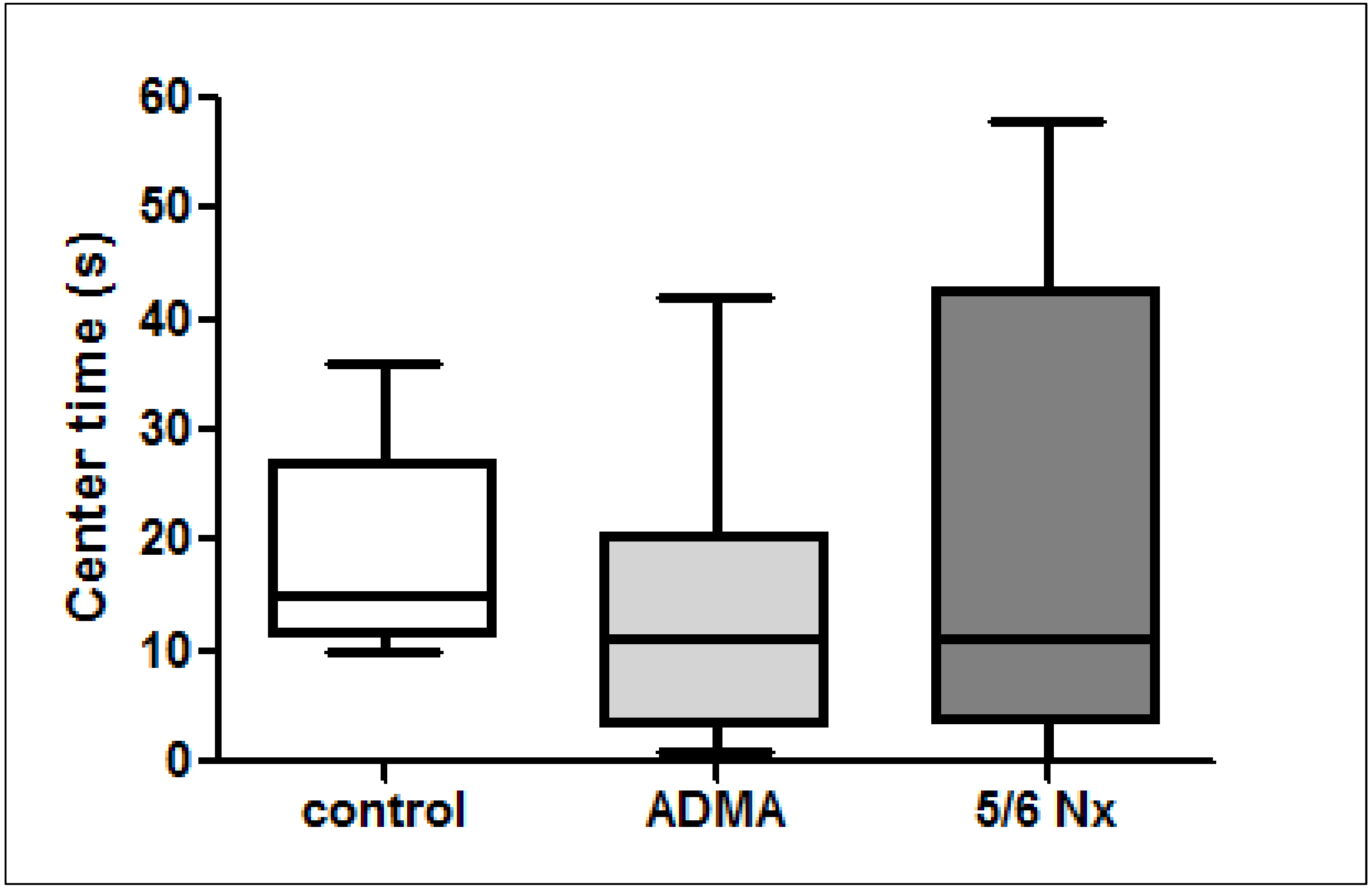
# Asymmetric dimethylarginine may mediate increased heat pain threshold in experimental chronic kidney disease

**KIELSTEIN et al.** ***Nephrol Dial Transplant. 2011 Nov 29***



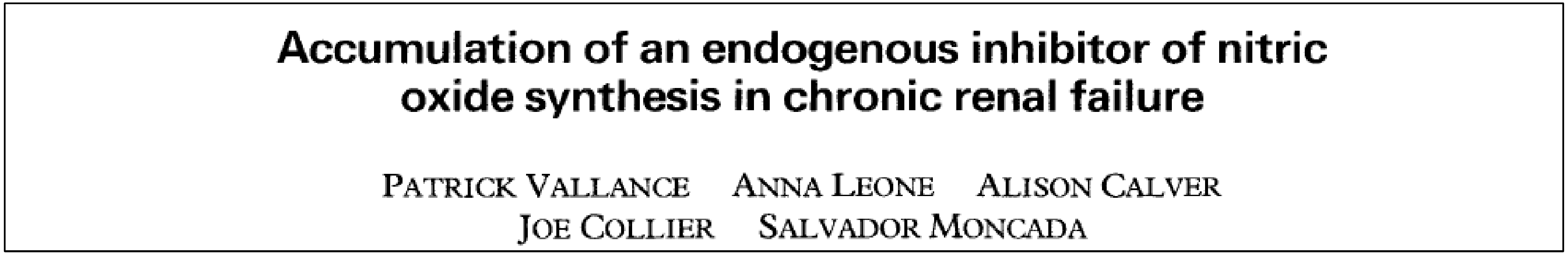
Medizinische Hochschule Hannover

# Center time



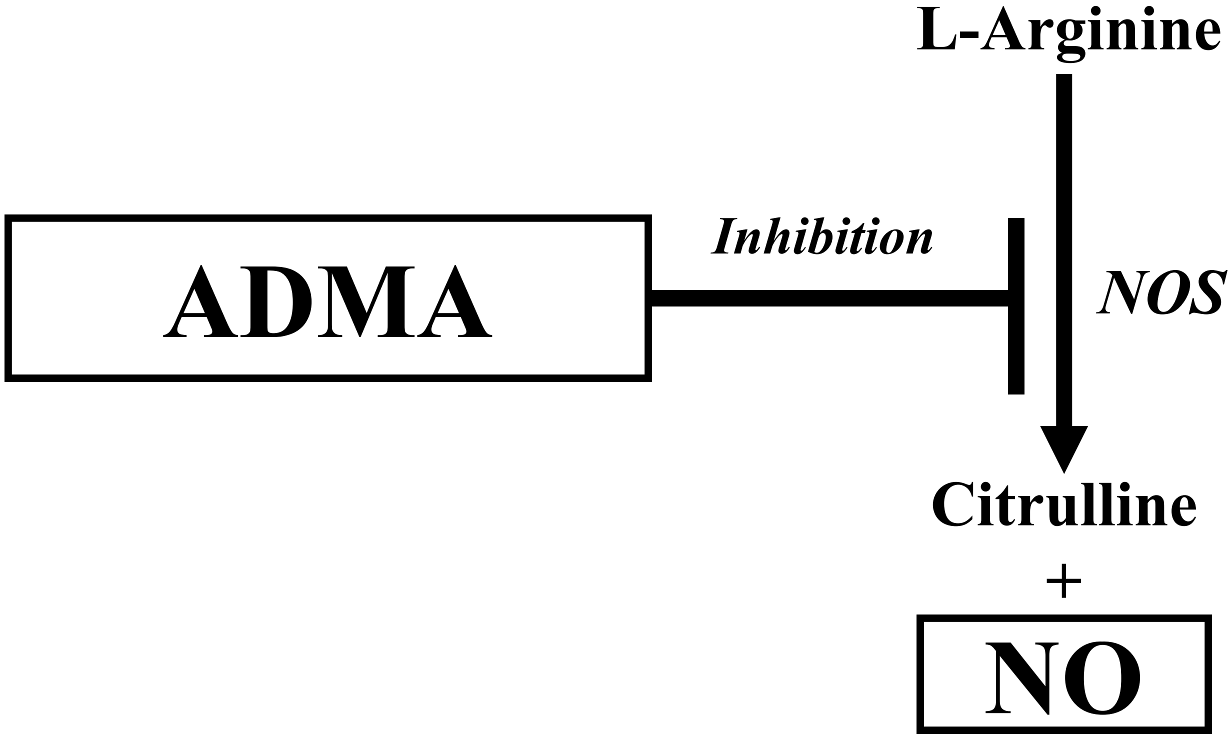
# ADMA and NO

VALLANCE et al. *Lancet* 339: 572-575, 1992



**Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure**

PATRICK VALLANCE ANNA LEONE ALISON CALVER
JOE COLLIER SALVADOR MONCADA



**L-Arginine**

**ADMA**

***Inhibition***

***NOS***

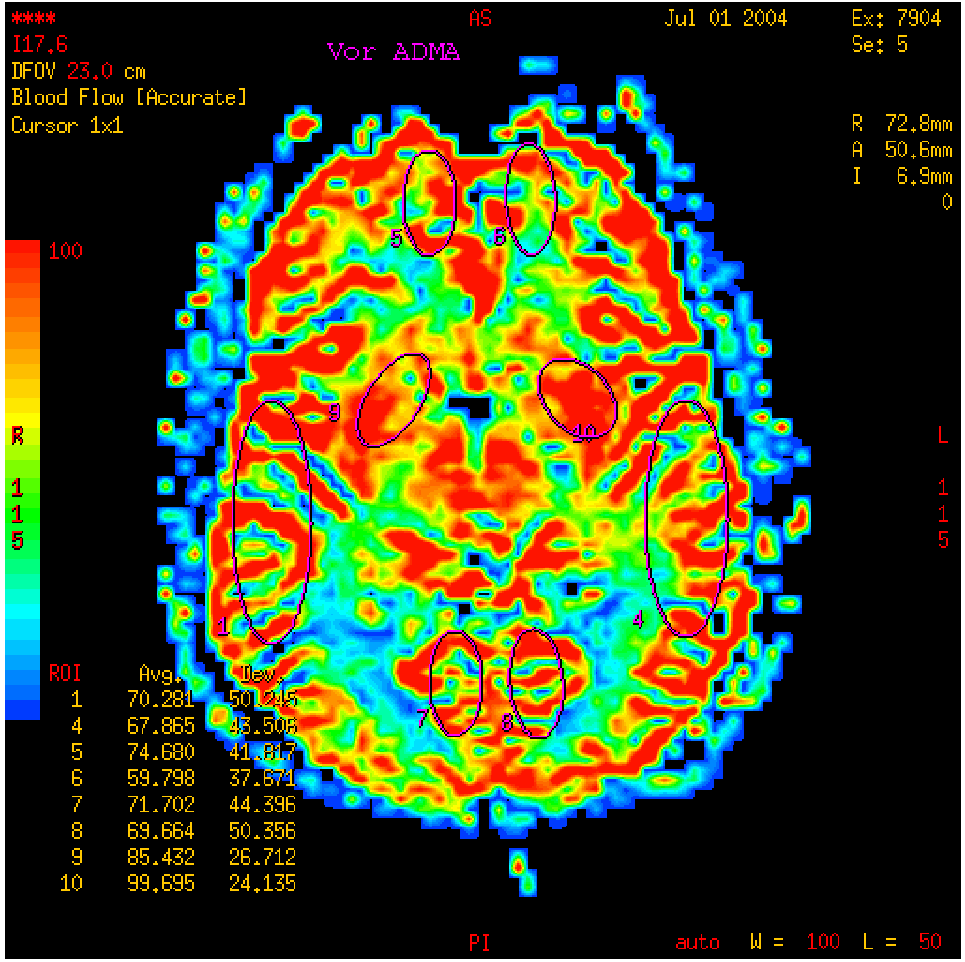
**Citrulline**

+

**NO**

# ADMA infusion decreases arterial compliance and cerebral blood flow in man

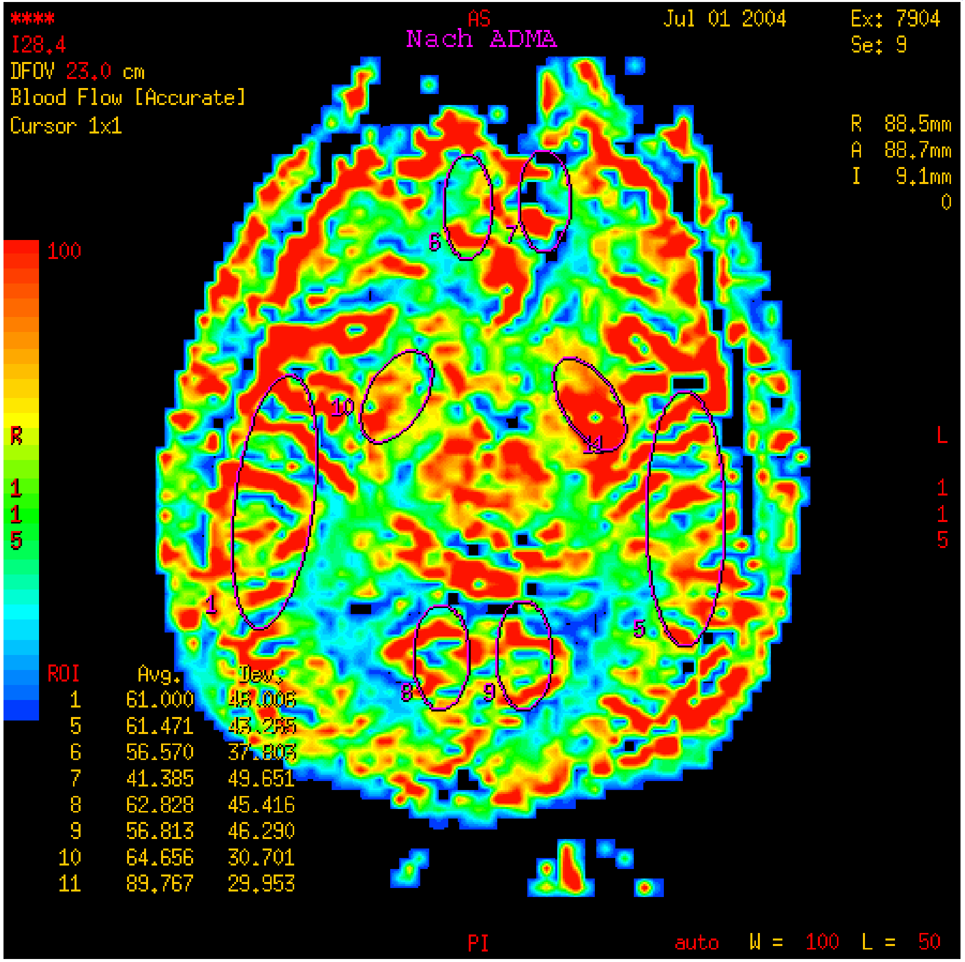
KIELSTEIN et al. *Stroke* 37(8):2024-9, 2006



****
AS
Jul 01 2004
Ex: 7904
I17.6
Vor ADMA
Se: 5
DFOV 23.0 cm
Blood Flow [Accurate]
Cursor 1x1
R 72.8mm
A 50.6mm
I 6.9mm
0
100
R
1
1
5
L
1
1
5
5
6
9
10
1
4
7
8
PI
auto W = 100 L = 50

```
ROI    Avg.     Dev.
 1    70.281   50.245
 4    67.865   43.505
 5    74.680   41.817
 6    59.798   37.671
 7    71.702   44.396
 8    69.664   50.356
 9    85.432   26.712
10    99.695   24.135
```

pre ADMA infusion



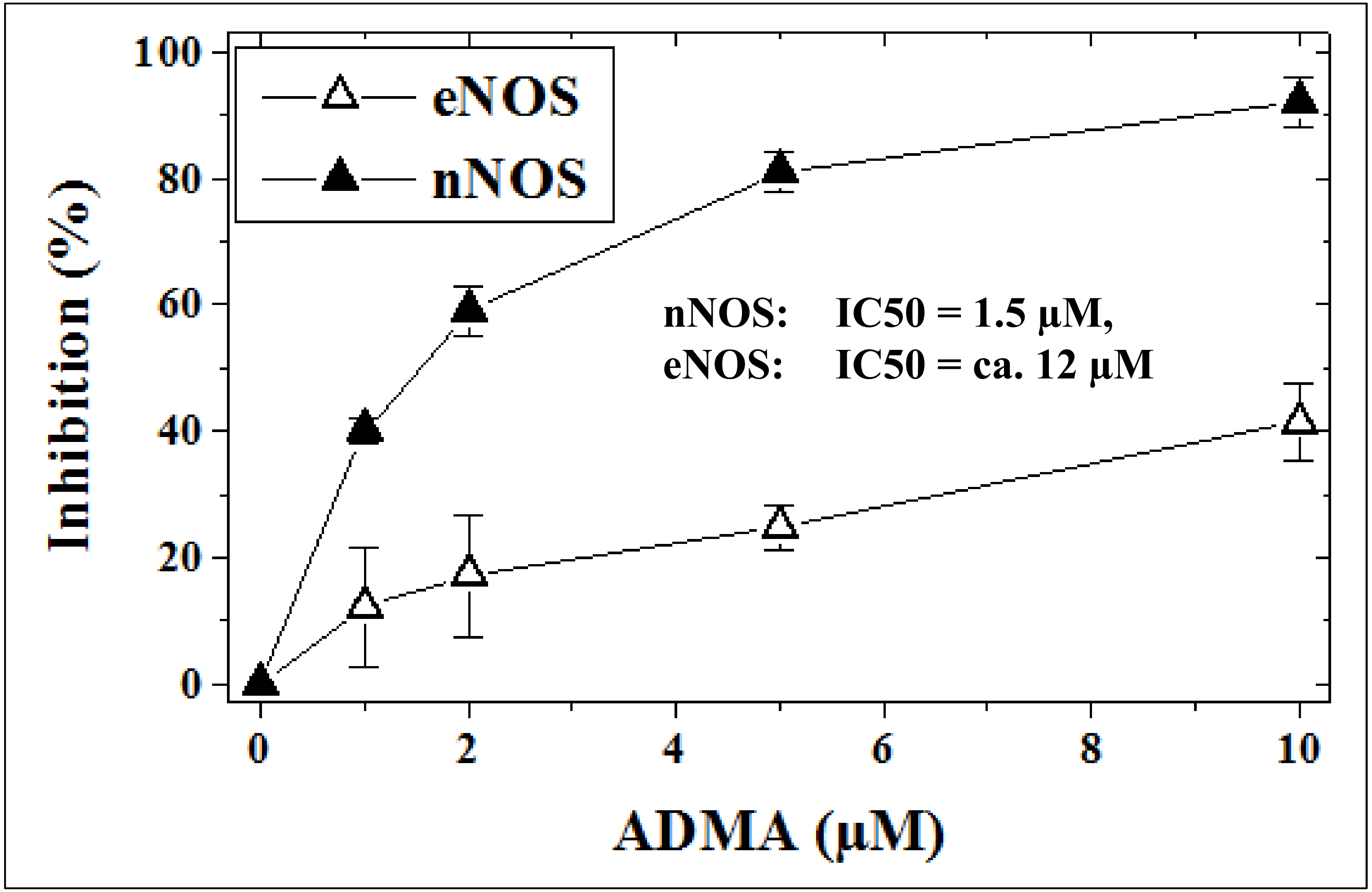
****
AS
Jul 01 2004
Ex: 7904
I28.4
Nach ADMA
Se: 9
DFOV 23.0 cm
Blood Flow [Accurate]
Cursor 1x1
R 88.5mm
A 88.7mm
I 9.1mm
0
100
R
1
1
5
L
1
1
5
6
7
10
11
1
5
8
9
PI
auto W = 100 L = 50

```
ROI    Avg.     Dev.
 1    61.000   48.006
 5    61.471   43.255
 6    56.570   37.803
 7    41.385   49.651
 8    62.828   45.416
 9    56.813   46.290
10    64.656   30.701
11    89.767   29.953
```

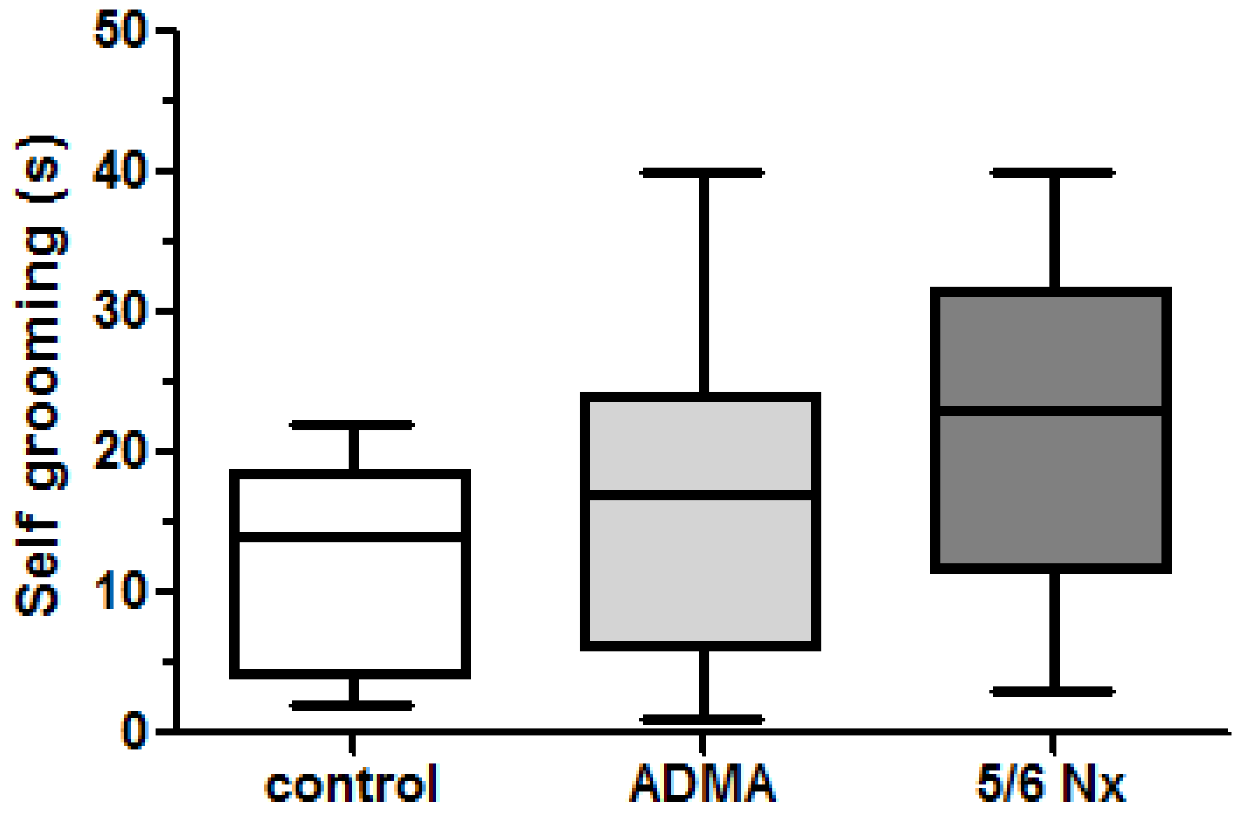
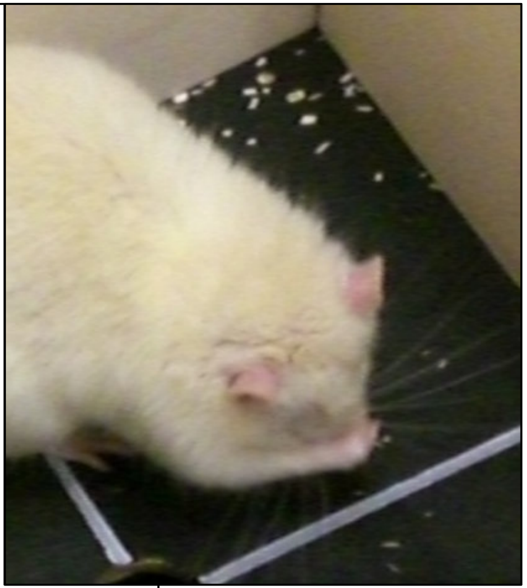
post ADMA infusion

# Asymmetric dimethylarginine (ADMA)--a modulator of nociception in opiate tolerance and addiction?

KIELSTEIN et al. *Nitric Oxide* 17(2):55-9, 2007



nNOS: IC50 = 1.5 µM,
eNOS: IC50 = ca. 12 µM

# Self grooming