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Stress und Depression – Einfluss genetischer Faktoren

12. Jahrestagung der DGBS in Hannover
29. September 2012

Marcus Ising

Stress und Depression – Einfluss genetischer Faktoren

1) Depression – Eine Stresserkrankung

Early Developmental Stages of Psychopathology Study: Risk Factors for MDE Onset

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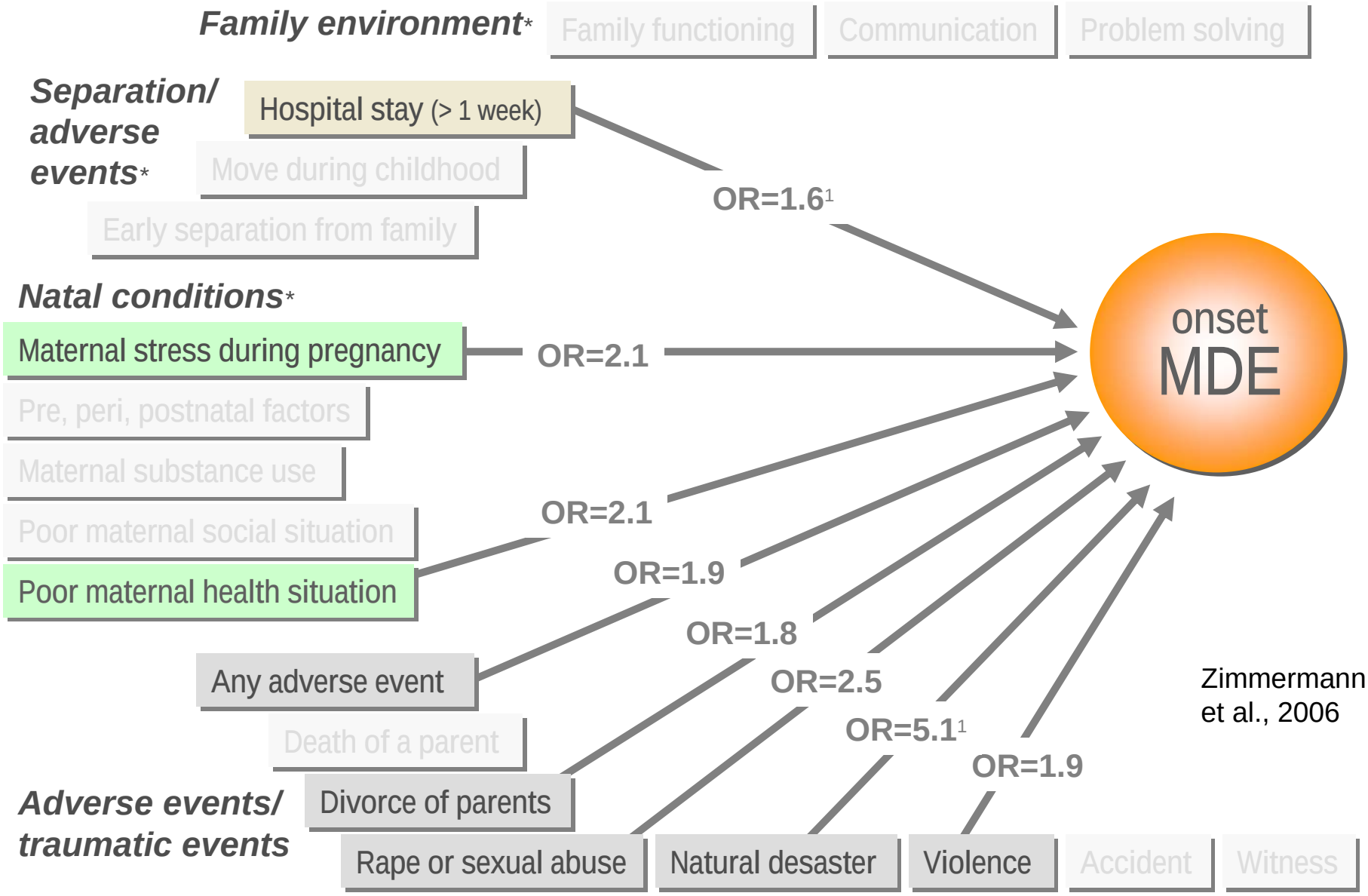

Zimmermann et al., 2006

Plasma Cortisol Levels and Circadian Rhythm

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- Elevated plasma cortisol and attenuated circadian cortisol rhythms in depressed patients compared with normal subjects (Sachar, 1976).

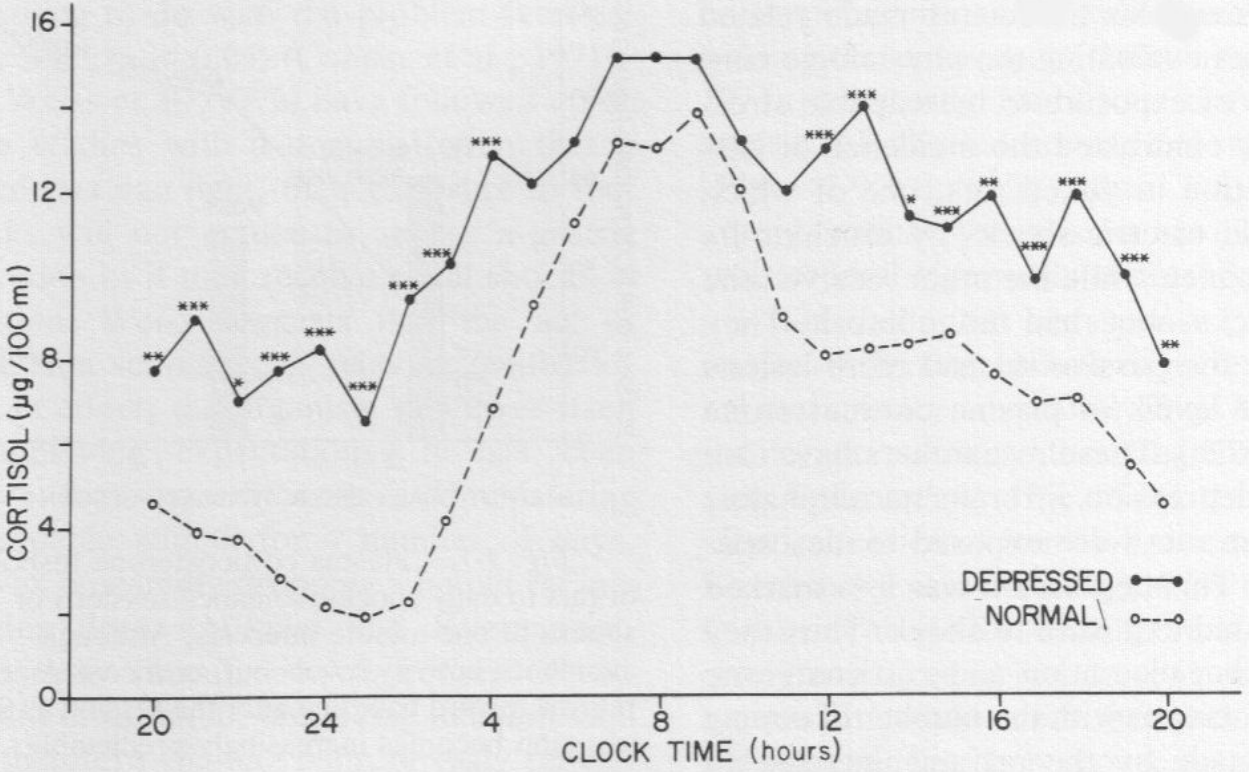

Fig. 7-6. Mean hourly plasma cortisol concentration over a 24-hour period for seven depressed patients compared with the mean for 54 normal subjects. Each point represents the mean cortisol concentration during the preceding hour: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *(Sachar, 1976).*

Impaired Stress Hormone Regulation in Acute Depression

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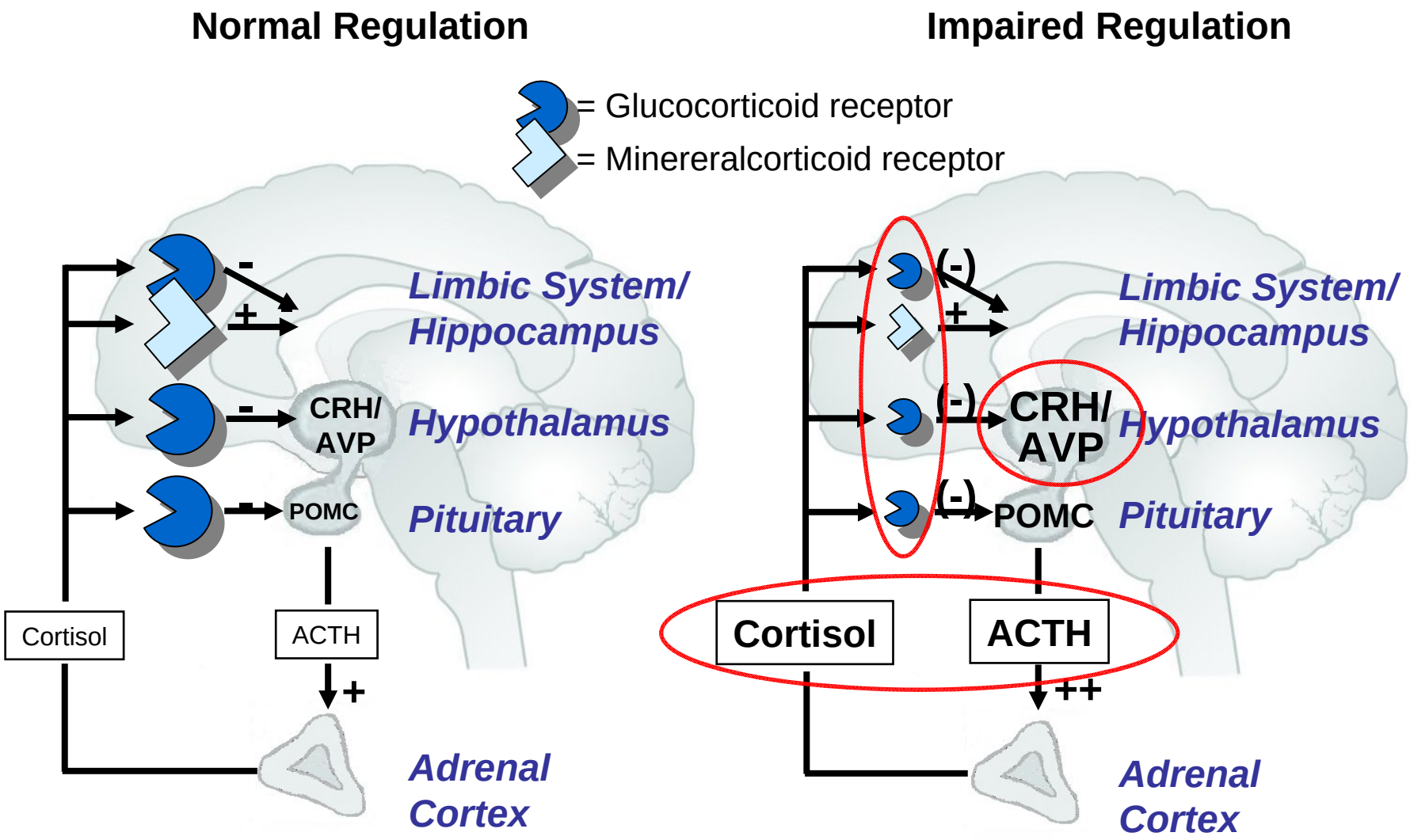

Ising & Holsboer, Dial. Clin. Neurosc., 2006

Combined Dex/CRH Test to Evaluate Impaired Stress Hormone Regulation

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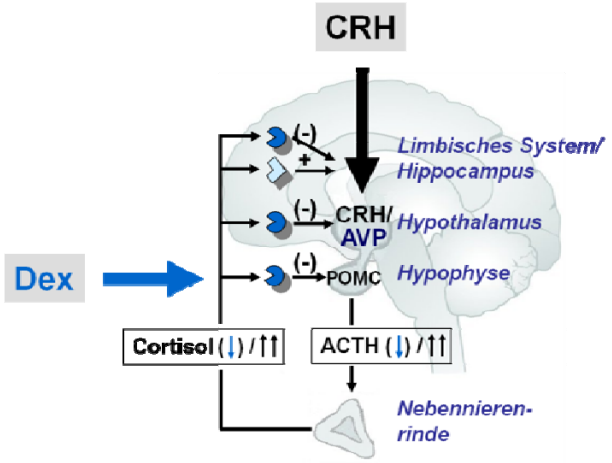
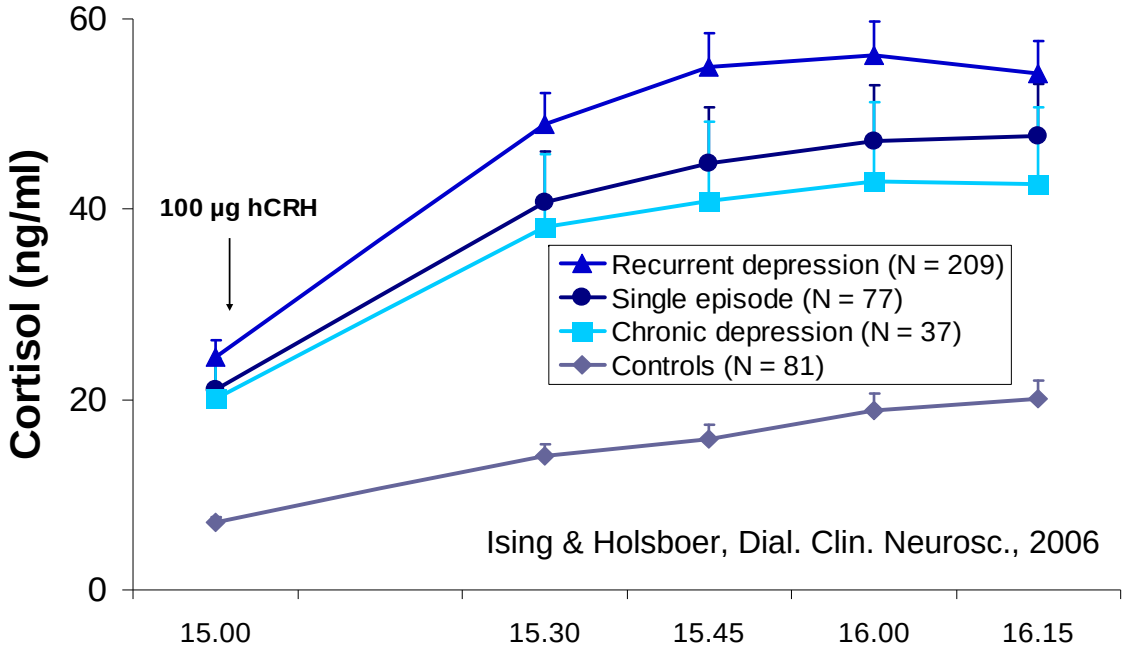
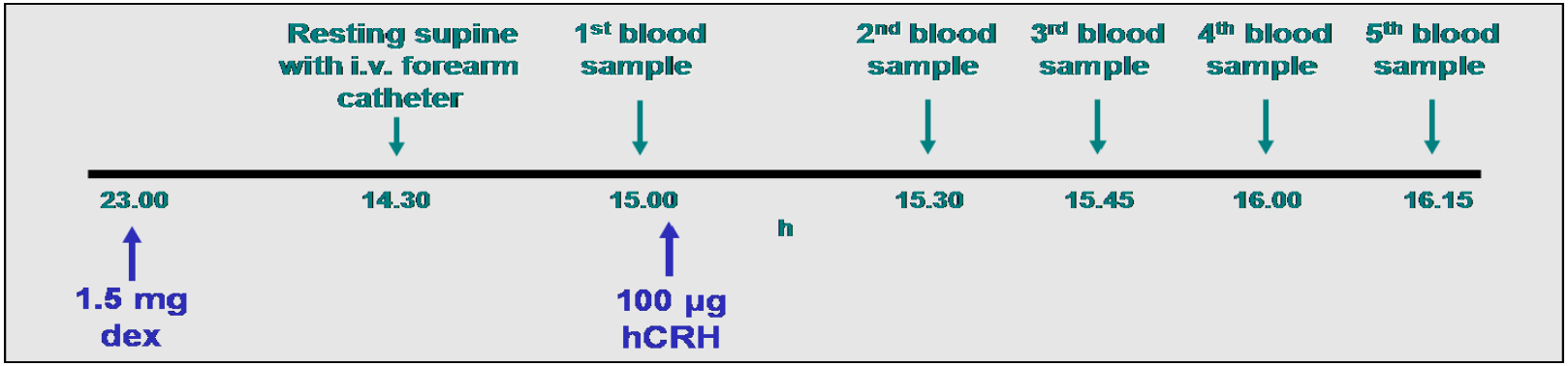
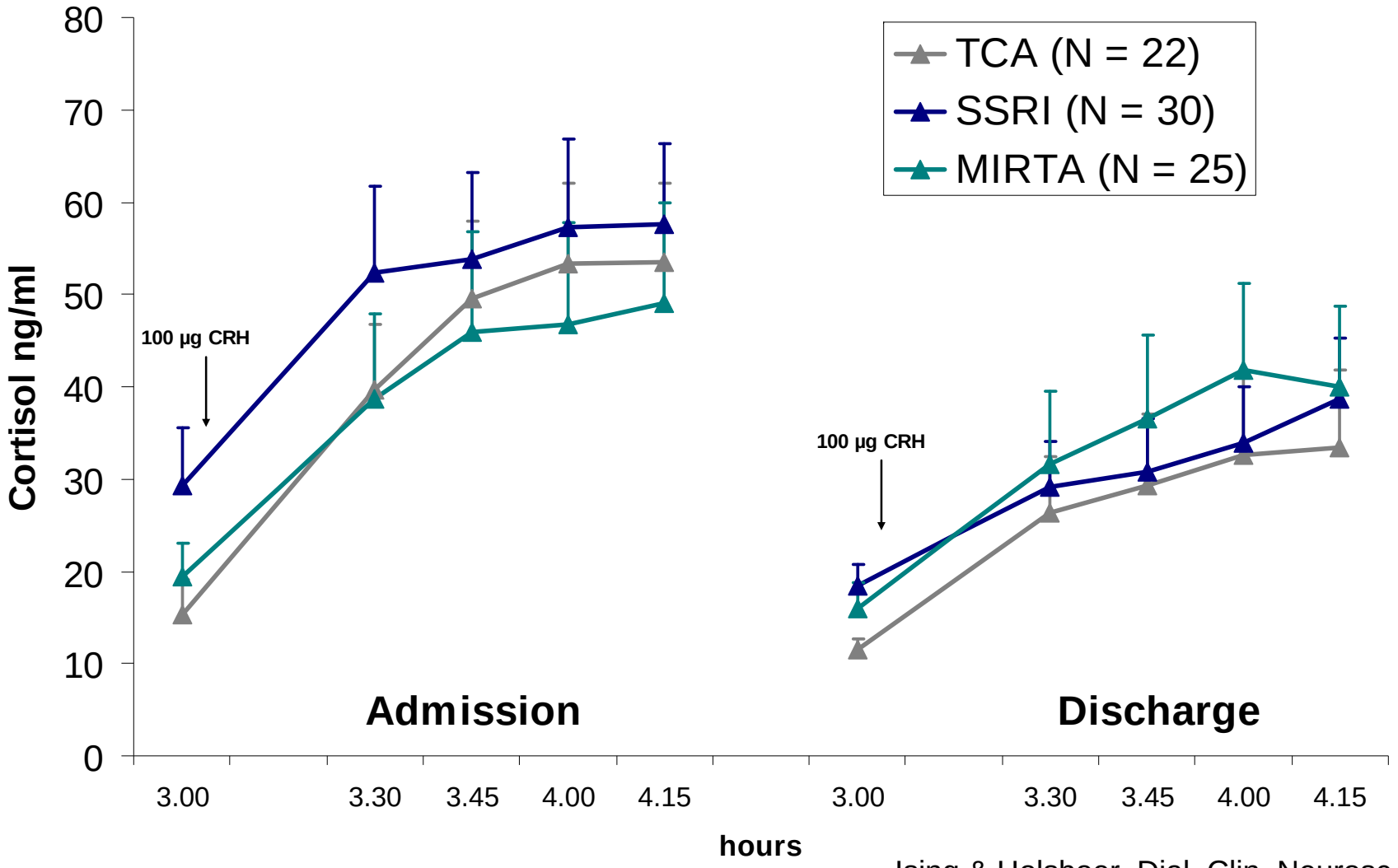




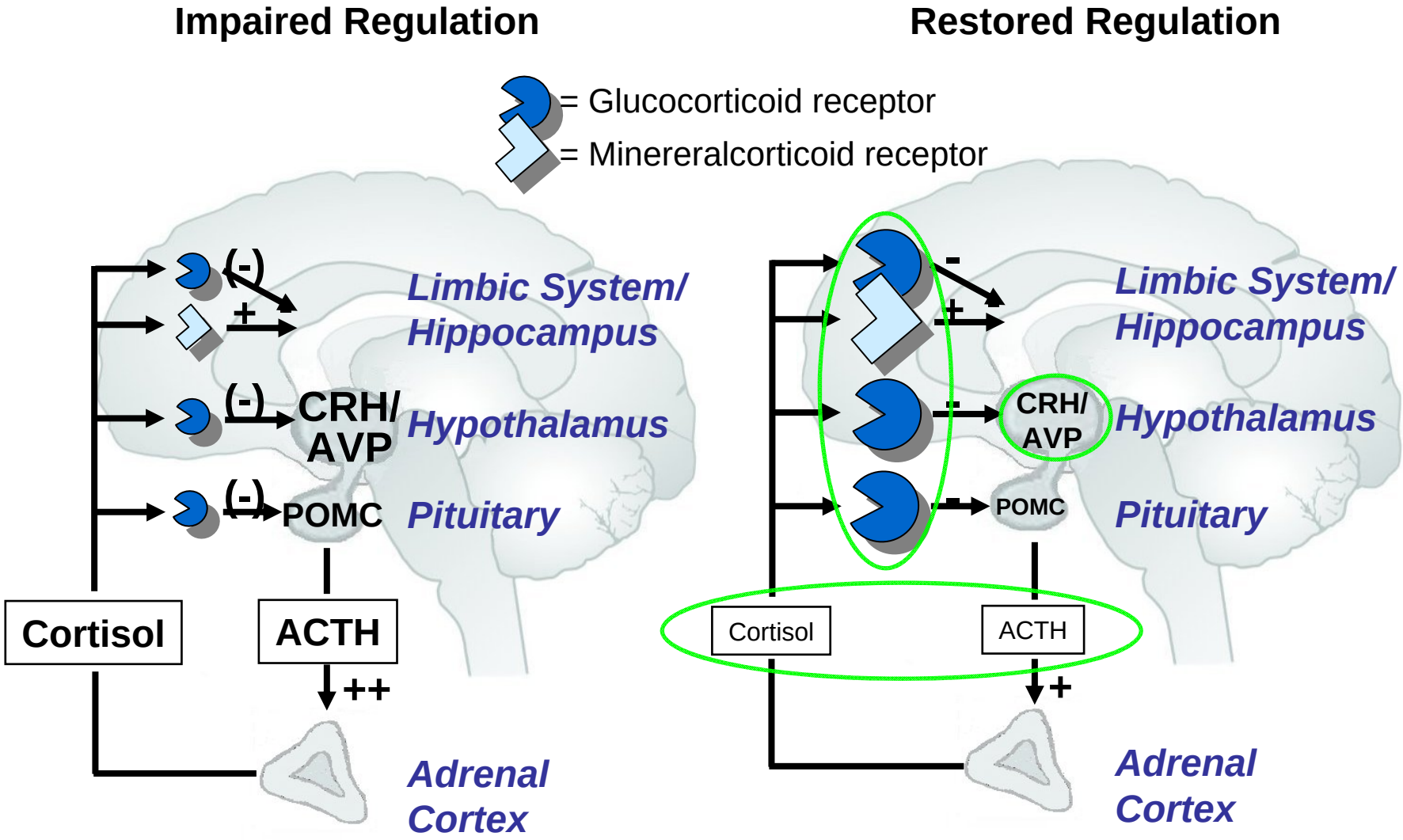


Impaired Stress Hormone Regulation Resolves under Monoaminergic Treatment …



Ising & Holsboer, Dial. Clin. Neurosc., 2006

… Suggesting a Restoration of the Glucocorticoid Receptor Function



Ising & Holsboer, Dial. Clin. Neurosc., 2006

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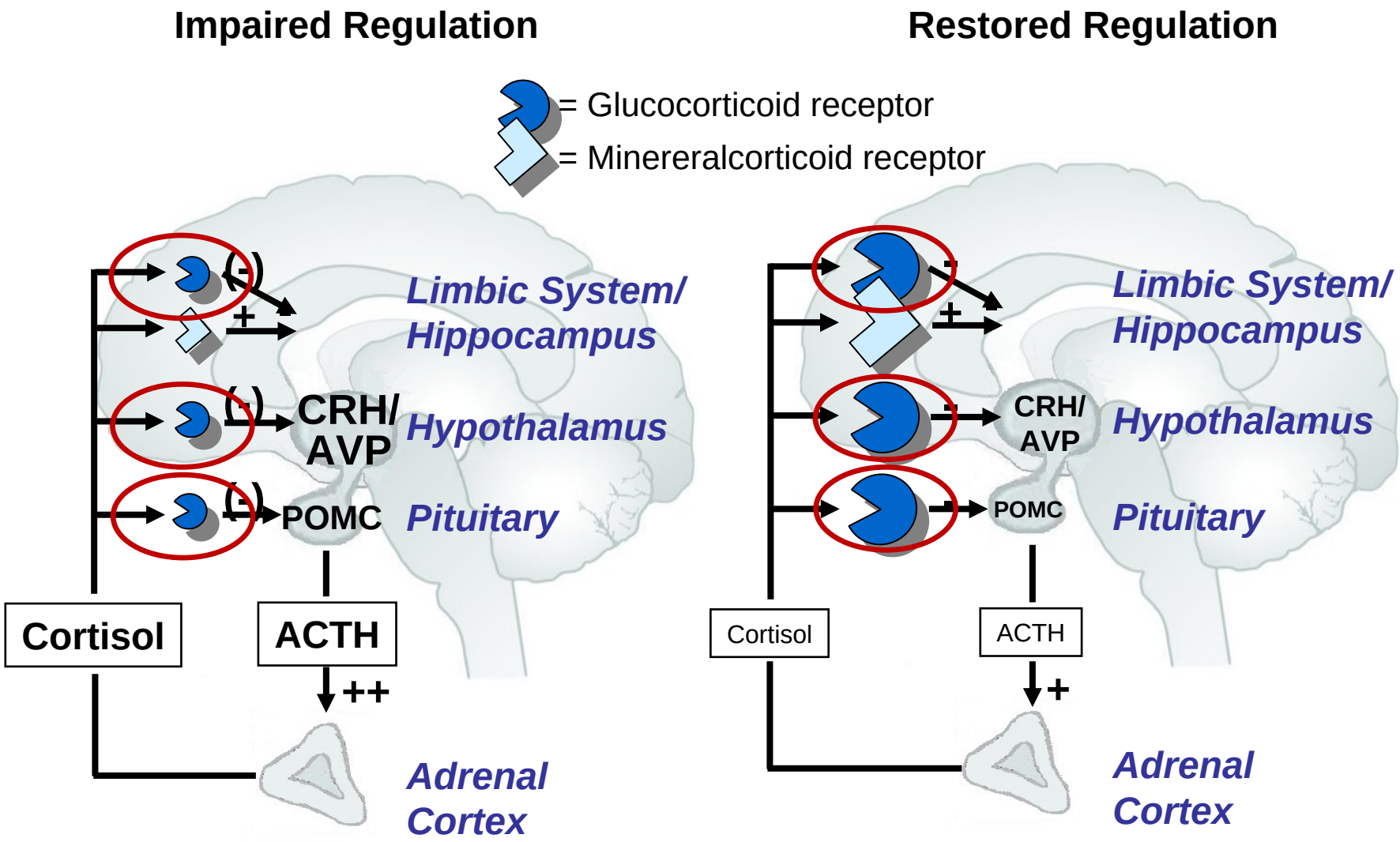
2) Genetik der Stresshormonachse und der Circadianen Rhythmik

Genes Involved in Stress Hormone Regulation



Ising & Holsboer, Dial. Clin. Neurosc., 2006

Glucocorticoid Receptor Complex

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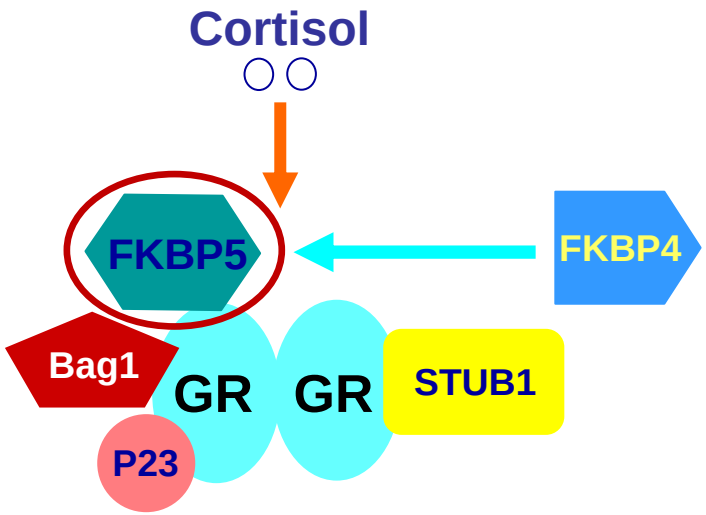
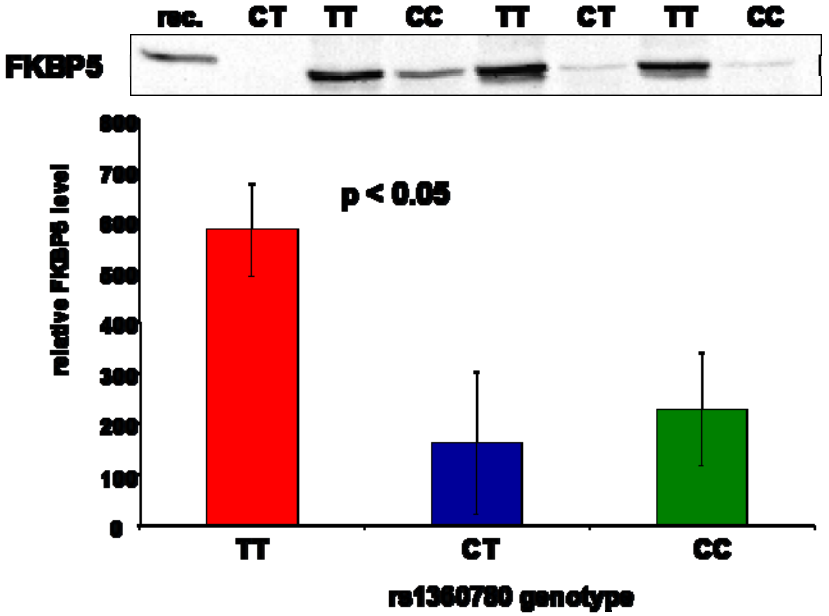
- The glucocorticoid receptor (GR) is a complex structure involving a number of “assistant” proteins, so-called chaperons, moderating glucocorticoid binding and GR translocation into the nucleus. Among all chaperones, FKBP5 seems to be of special importance preventing GR translocation.
- The FKBP5 gene comprises only a single major LD block including mainly intronic SNPs. Nevertheless, these SNPs influence FKBP5 protein levels, presumably, due to linkage with a yet unknown functional variant.





Binder et al., Nat. Gen., 2004

Polymorphisms in the FKBP5 Gene Affect Risk for Depression in Traumatized Subjects

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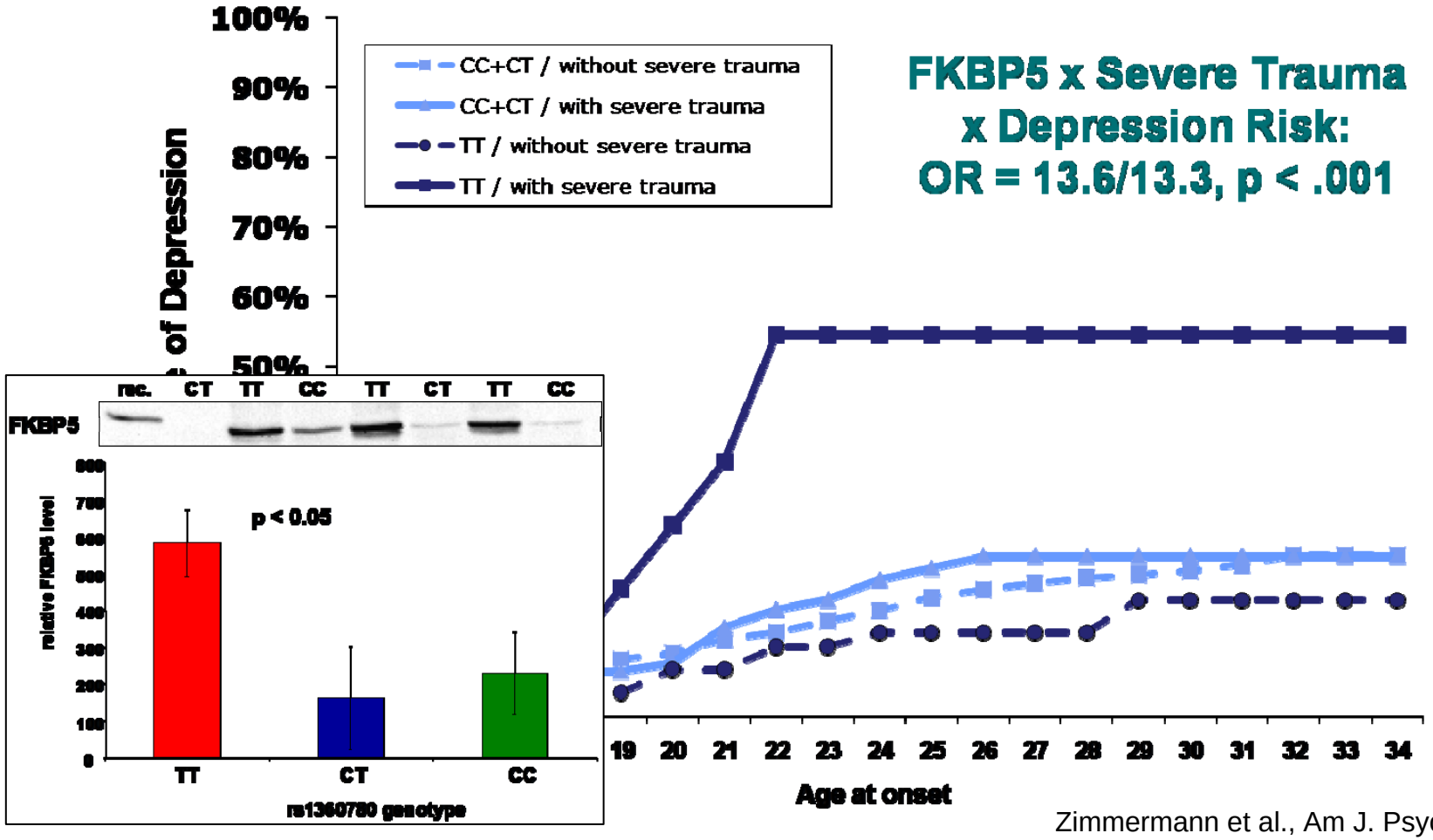
- The FKBP5 genotype (rs1360780) associated with increased FKBP5 activity predicts an increased depression risk, but only for those subjects previously exposed to traumatic events.



Zimmermann et al., Am J. Psychiat., 2011

Polymorphisms in the FKBP5 Gene Affect Antidepressant Treatment Outcome

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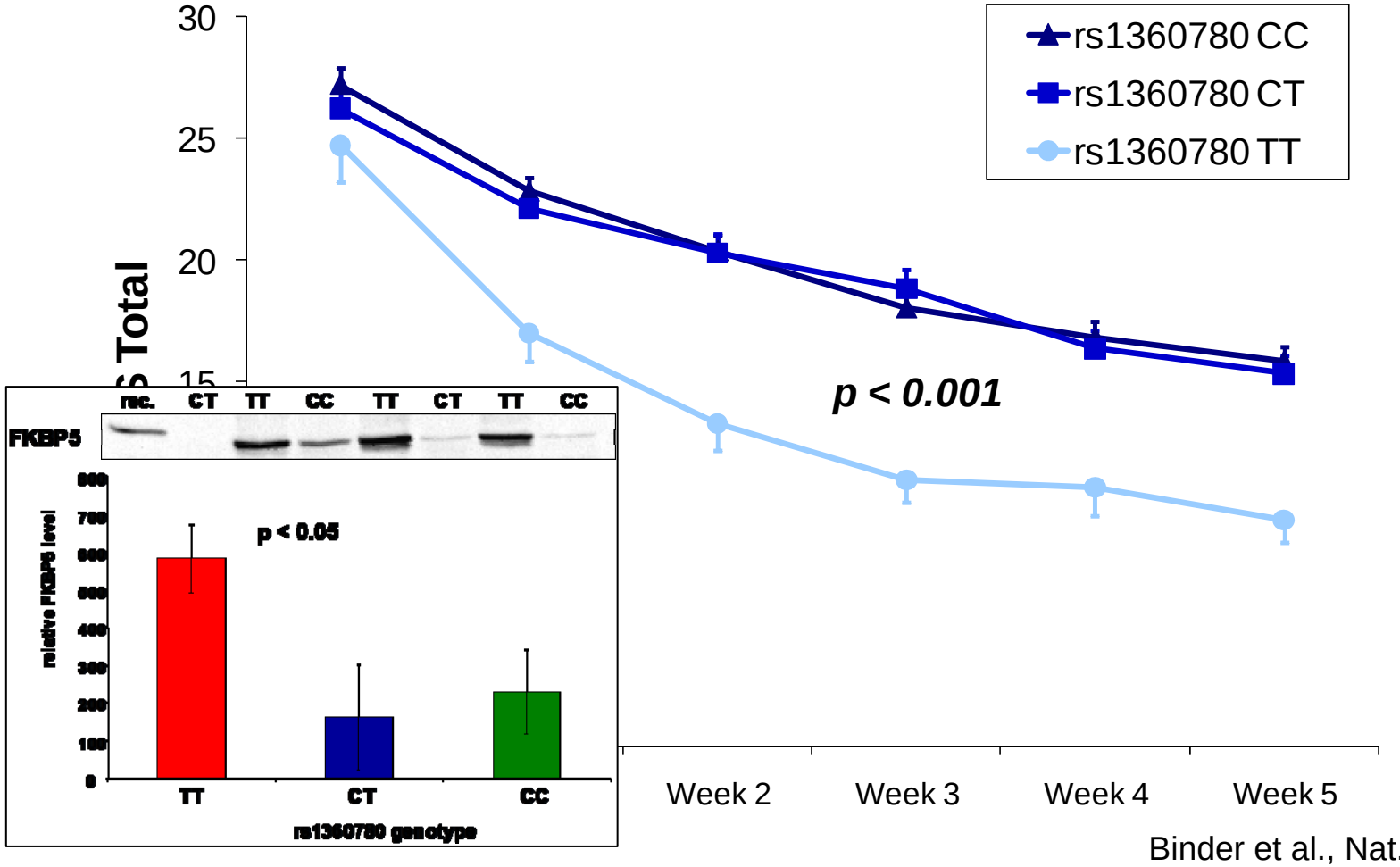
- The same FKBP5 genotype (rs1360780) associated with increased depression risk also predicts also antidepressant treatment outcome.



Binder et al., Nat. Gen., 2004

Plasma Cortisol Levels and Circadian Rhythm

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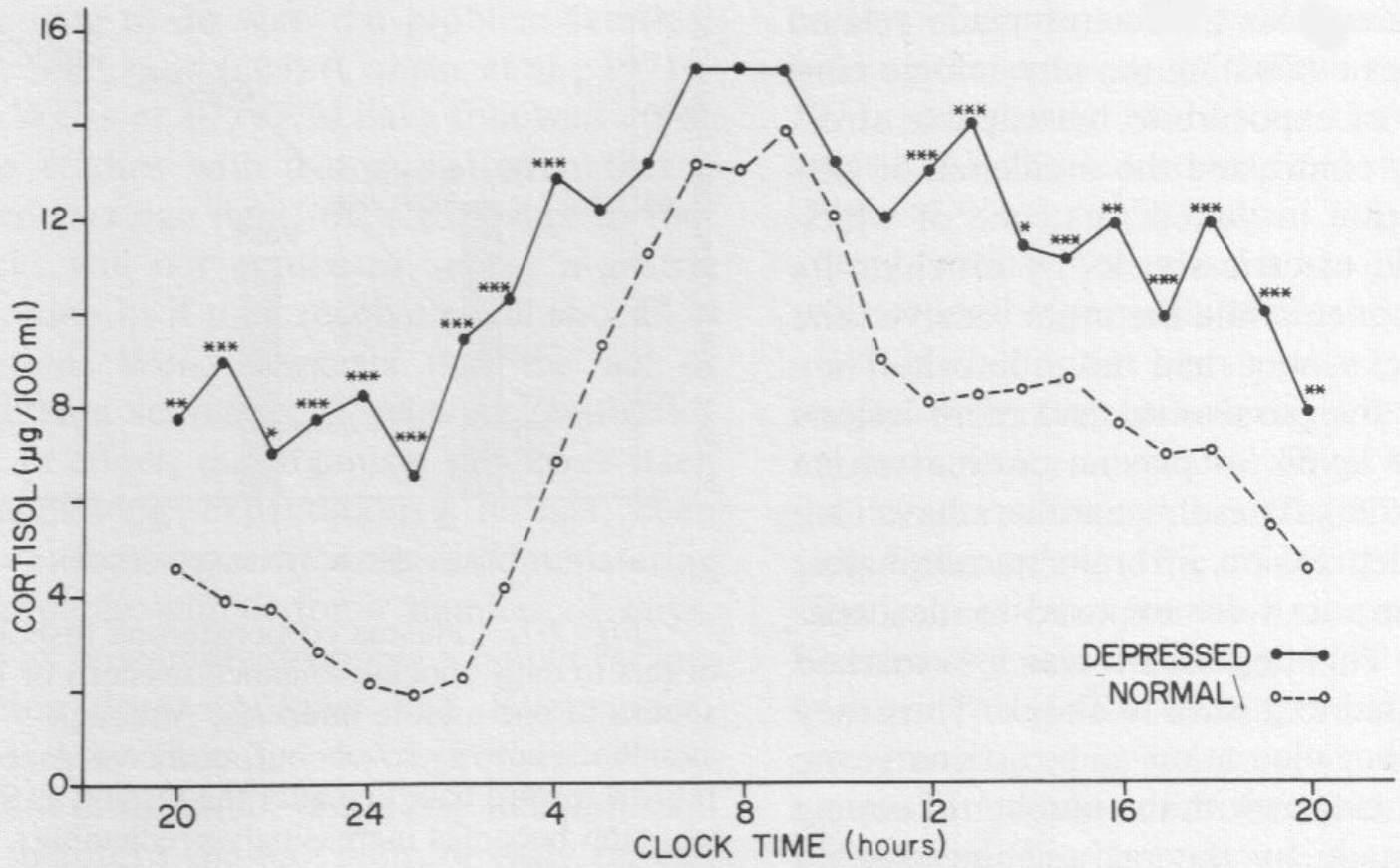

Fig. 7-6. Mean hourly plasma cortisol concentration over a 24-hour period for seven depressed patients compared with the mean for 54 normal subjects. Each point represents the mean cortisol concentration during the preceding hour: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *(Sachar, 1976)*.

Circadian Rhythms in Depression

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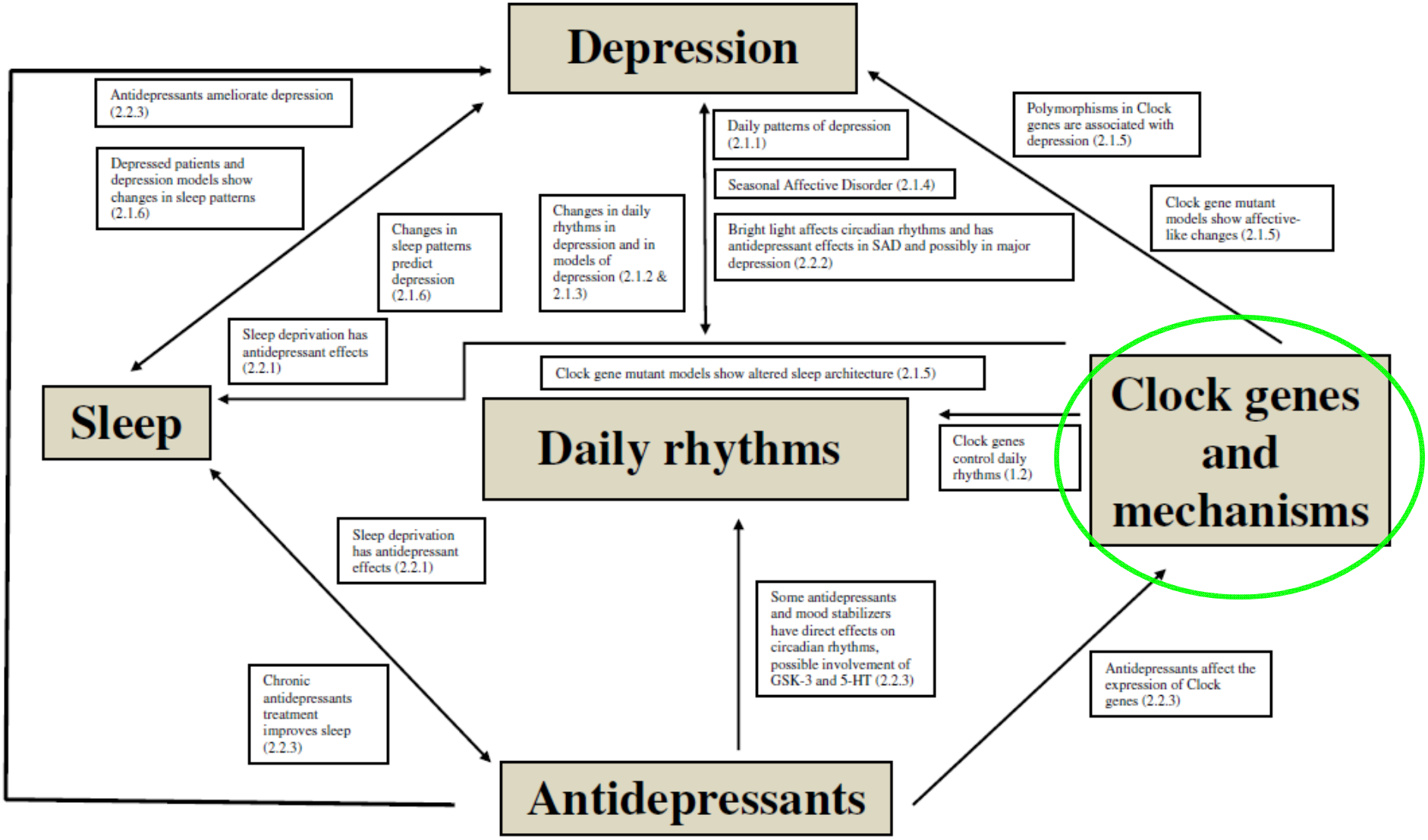

Kronfeld-Schor & Einat, Neuropharm., 2012

Primary “Clock Gene” Loops

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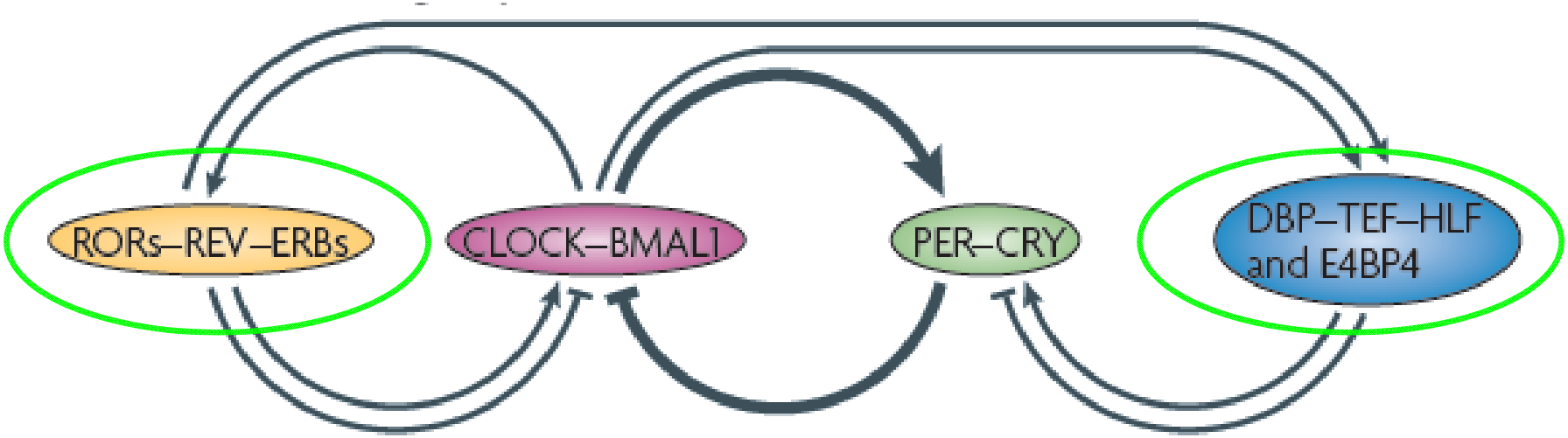
- Clock proteins compose regulatory loops, with CLOCK, BMAL1, PER and CRY constituting the primary feedback loop.
- CLOCK and BMAL1 activate PER and CRY, which in turn suppress CLOCK and BMAL1. Transcriptional activators RORs and DBP–TEF–HLF and repressors REV–ERBs and E4BP4 synergistically modify the expression of primary clock proteins, conferring a robust transcriptional regulation to the clock



Zhang & Kay, Nat. Rev. MolCellBio., 2010

Stress und Depression – Einfluss genetischer Faktoren

3) „Clock Genes“, Stresshormonregulation und Depressionsrisiko

“Clock Genes” and Affective Disorders

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Table 2 Studies reporting suggestive associations between circadian genes and mood spectrum disorders BD: bipolar disorder, UD: unipolar disorder, SAD: seasonal affective disorder.

Gene	OMIM nomenclature	Studies reporting suggestive associations		
		BD	UD Major depression	SAD
CLOCK	CIRCADIAN LOCOMOTOR OUTPUT CYCLES KAPUT	(Kripke et al., 2009; Lee et al., 2010; Shi et al., 2008; Soria et al., 2010b)	(Soria et al., 2010b)	
NPAS2	NEURONAL PAS DOMAIN PROTEIN 2	(Kripke et al., 2009; Mansour et al., 2009; Soria et al., 2010b)	(Soria et al., 2010b)	(Johansson et al., 2003; Partonen et al., 2007)
ARNTL1	ARYL HYDROCARBON RECEPTOR NUCLEAR TRANSLOCATOR-LIKE 1 (BMAL1)	(Mansour et al., 2006, 2009; Nievergelt et al., 2006; Soria et al., 2010b)	(Soria et al., 2010b; Utge et al., 2010)	(Partonen et al., 2007)
ARNTL2	ARYL HYDROCARBON RECEPTOR NUCLEAR TRANSLOCATOR-LIKE 2 (BMAL2)	(Soria et al., 2010b)	(Soria et al., 2010b)	
PER1	PERIOD HOMOLOG 1 (DROSOPHILA)	(Kripke et al., 2009)		
PER2	PERIOD HOMOLOG 2 (DROSOPHILA)	(Kripke et al., 2009)	(Soria et al., 2010b)	(Partonen et al., 2007)
PER3	PERIOD HOMOLOG 3 (DROSOPHILA)	(Mansour et al., 2006; Nievergelt et al., 2006; Soria et al., 2010b)	(Soria et al., 2010b)	
CRY1	CRYPTOCHROME 1	(Soria et al., 2010b)	(Soria et al., 2010b)	
CRY2	CRYPTOCHROME 2	(Mansour et al., 2009)		(Lavebratt et al., 2010)
TIMELESS	TIMELESS HOMOLOG (DROSOPHILA)	(Mansour et al., 2006)	(Utge et al., 2010)	
NR1D1	NUCLEAR RECEPTOR SUBFAMILY 1, GROUP D, MEMBER 1	(Kishi et al., 2008; Kripke et al., 2009; Severino et al., 2009) *	(Soria et al., 2010b)	
RORA	RAR-RELATED ORPHAN RECEPTOR A	(Soria et al., 2010b)	(Utge et al., 2010)	
RORB	RAR-RELATED ORPHAN RECEPTOR B	(Mansour et al., 2009; McGrath et al., 2009)		
CSNK1δ	CASEINE KINASE I DELTA	(Kripke et al., 2009)		
CSNK1ε	CASEINE KINASE I EPSILON	(Mansour et al., 2009; Shi et al., 2008; Soria et al., 2010b)	(Utge et al., 2010)	
GSK3β	GLYCOGEN SYNTHASE KINASE 3-BETA	(Szczepankiewicz et al., 2006) *		
DBP	D SITE OF ALBUMIN PROMOTER-BINDING PROTEIN		(Soria et al., 2010b)	
BHLHB2	BASIC HELIX-LOOP-HELIX DOMAIN CONTAINING, CLASS B, 2	(Shi et al., 2008)		
BHLHB3	BASIC HELIX-LOOP-HELIX DOMAIN CONTAINING, CLASS B, 3	(Soria et al., 2010b)		
ASMT	ACETYLSEROTONIN METHYLTRANSFERASE, X-CHROMOSOMAL		(Galecki et al., 2010)	
MTNR1B	MELATONIN RECEPTOR 1B		(Galecka et al., in press)	
AANAT	ARYLALKYLAMINE N-ACETYLTRANSFERASE		(Soria et al., 2010a)	
PPARGC1B	PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA, COACTIVATOR 1, BETA	(Kripke et al., 2009)		

*: association observed only for females with bipolar disorders (Kishi et al., 2009; Szczepankiewicz et al., 2006).

Etain et al.,
Europ. Neuropsychopharm., 2011

Clock Gene Associations with the Combined Dex/CRH Test

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- 350 acutely depressed inpatients of the Munich Antidepressant Response Signature (MARS) project participating in a combined dex/CRH test during the first 10 days after clinic admission have been genotyped for the following 18 clock genes.

- ***ARNTL2***
- ***BHLHB2***
- ***CLOCK***
- ***CRY1, CRY2***
- ***CSNK1D, E***
- ***GSK3B***
- ***MTNR1A, 1B***
- ***NPAS2***
- ***NR1D1***
- ***PER1, 2, 3***
- ***RORA, RORB***
- ***TIMELESS***

Results of the Genetic Association Analysis

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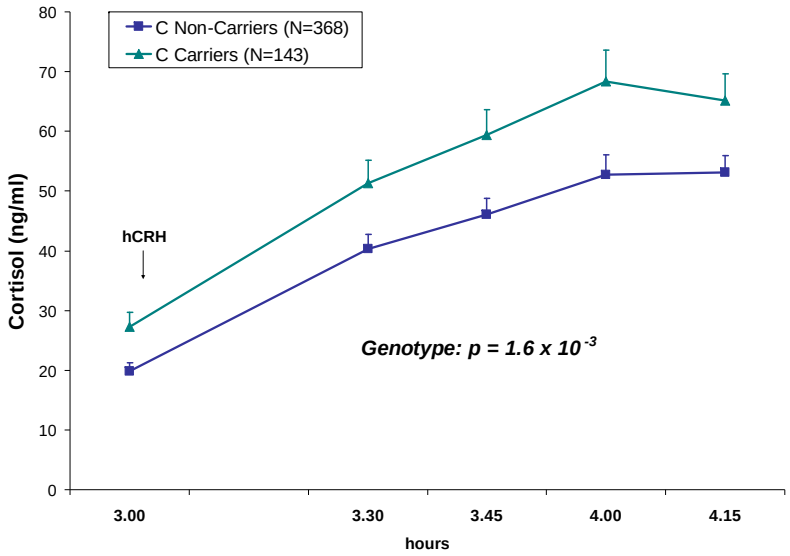
- Controlled for population stratification, 37 SNPs within eight genes showed nominal significant association with the cortisol response in the combined dex/CRH test.

  - ***BHLHB2: 1x 5‘UTR***
  - ***CLOCK: 1x intronic***
  - ***CSNK1E: 2x 5‘UTR***
  - ***GSK3B: 2x intronic, 1x 5‘UTR***
  - ***MTNR1A: 1x intronic***
  - ***NPAS2: 1x intronic***
  - ***RORA: 24x intronic, 2x 5‘UTR***
  - ***RORB: 1x intronic, 1x 5‘UTR***

- Most consistent associations were found for ***RORA***, expressing RAR-related orphan receptor alpha, which is a transcriptional activator of the primary clock gene loop.

- The strongest association was observed for the intronic SNP rs17204910 located in ***RORA***: p = 1.6 10^{-3}.



Effects of RORA (rs17204910) on Depression Risk and Antidepressant Treatment Outcome

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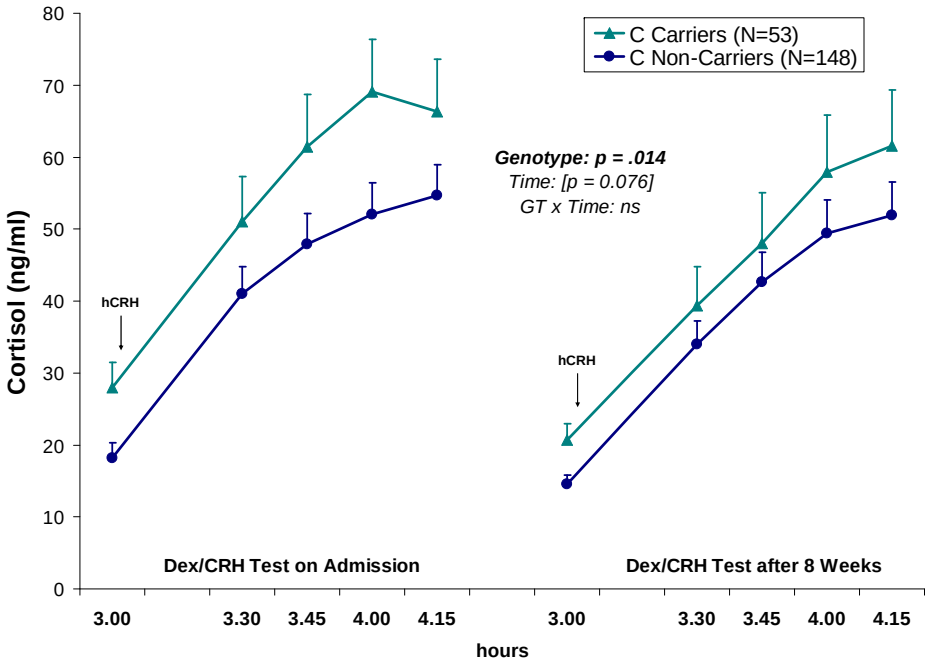
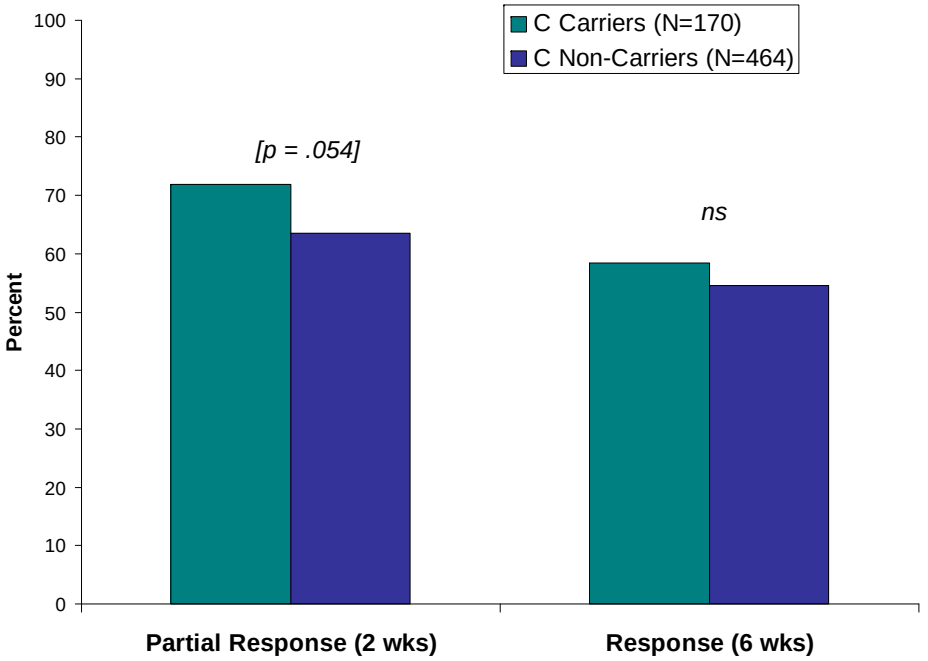
- Besides its effect on stress hormone regulation, rs17204910 (RORA) shows substantial effects on depression risk: ***RR = .71 (protective C allele), p = .005 (N=711/540)***.
- However: no effect on change in stress hormone regulation and [almost] no effect on antidepressant treatment outcome.





Effects of FKBP5 on Stress Hormone Regulation and Antidepressant Treatment Outcome

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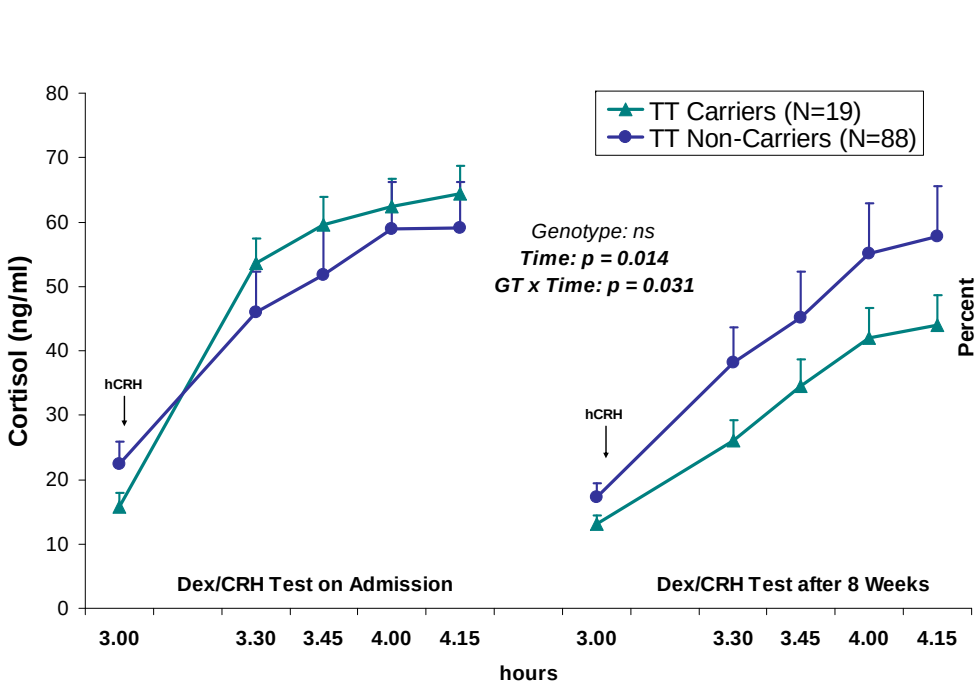
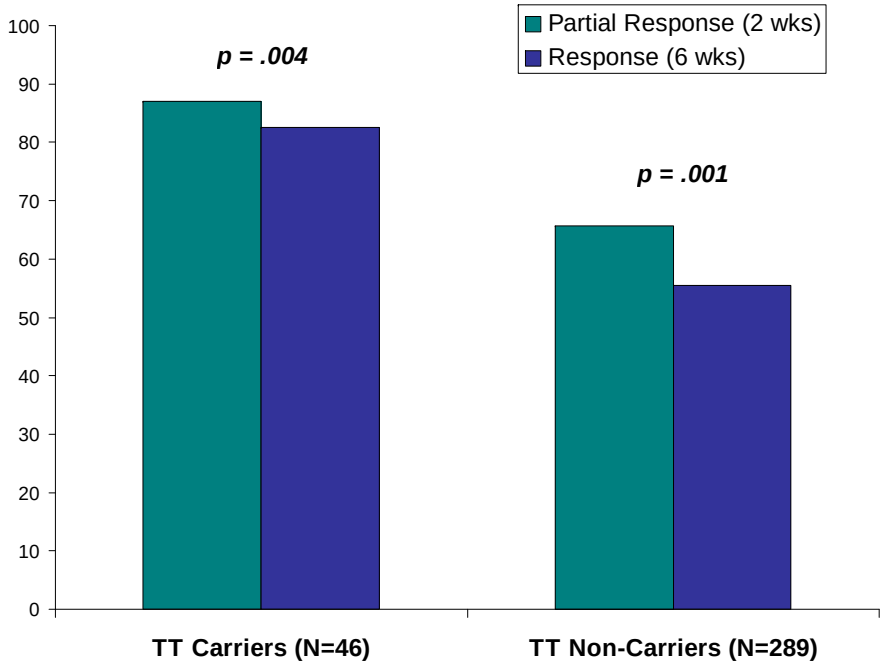
- In contrary to RORA, the FKBP5 variant rs1360780 shows profound effects on both, change in stress hormone regulation and antidepressant treatment outcome.





Stress und Depression – Einfluss genetischer Faktoren

4) Zusammenfassung und Einordnung der Ergebnisse

Key Messages

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1) ***Depression – A Stress-related Disorder***

- **Chronic tress and intensive trauma are risk factors for depression.**
- **Acute depression is characterized by an impaired stress hormone regulation and a disturbance of circadian rhythms.**

2) ***Genetics of Stress Hormone Regulation and Circadian Rhythms***

- **Strongest and most consistent genetic associations with stress hormone regulation and antidepressant treatment outcome have been shown for the FKBP5 gene moderating stress sensitivity.**
- **Circadian rhythms are primarily regulated by CLOCK, BMAL1, PER and CRY constituting the circadian feedback loop. These genes are regulated by further "clock genes" including the ROR gene family.**

3) ***"Clock Genes", Stress Hormone Regulation, and Depression Risk***

- **Most consistent associations with disturbed stress hormone regulation were observed for RORA.**
- **RORA variants are further associated with depression risk, but do not majorly predict monoaminergic antidepressant treatment outcome.**

Perspective of a Personalized Medicine Approach in Depression

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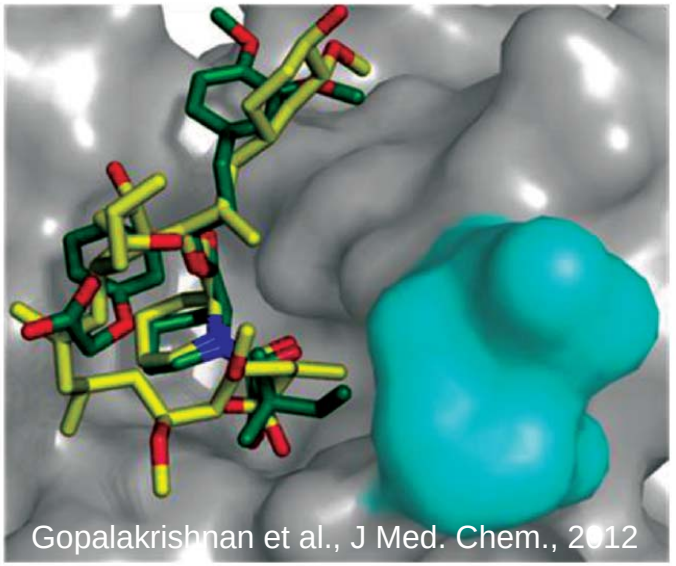
1) *FKBP5 driven Stress Hormone Dysregulation in Depression*

- Stress- associated impairment of stress hormone regulation
- Improves under monoaminergic antidepressant treatment
- Potentially best treated with treatments directed to improve stress hormone regulation



Gopalakrishnan et al., J Med. Chem., 2012

2) *Clock Genes driven Stress Hormone Dysregulation in Depression*

- Impaired stress hormone regulation due to disturbed chronobiology
- Does not improve under monoaminergic antidepressant treatment
- Potentially best treated with antidepressant medication directed against chronobiological disturbance

Studien-Team

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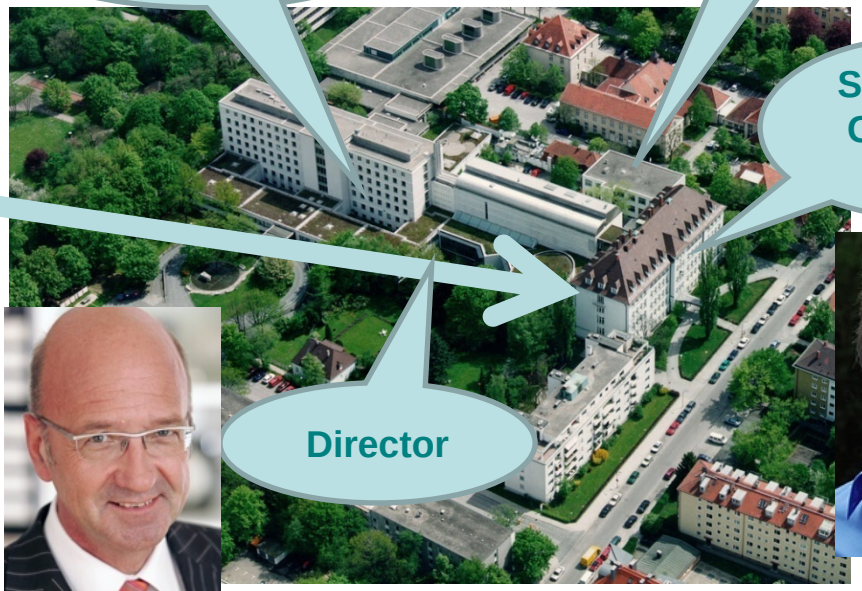
Study Coordinators

Lab & Genotyping



Statistical Genetics Group

Director