

Hjernens kemi som medspiller ved sund stresshåndtering: Serotonin-systemet og psykisk robusthed

Stresskonferencen, København 24. januar 2020

Vibe G. Frøkjær, MD, PhD
Senior consultant
Research associate professor



Neurobiology Research Unit,
Department of Neurology



Mental Health Services, Copenhagen



Copenhagen University



Vibe G. Frokjær
NRU, Copenhagen University Hospital, Rigshospitalet



Oversigt

- Kort kontekst
- Cases: Serotonin dynamik og mental sundhed
 - 1. Serotonin og stresss (kortisol) dynamik
 - 2. Serotonin og familiær risiko for depression
 - 3. Serotonin og tilpasning til årstider (vinter)
- Fortolkning, perspektiver og kliniske implikationer

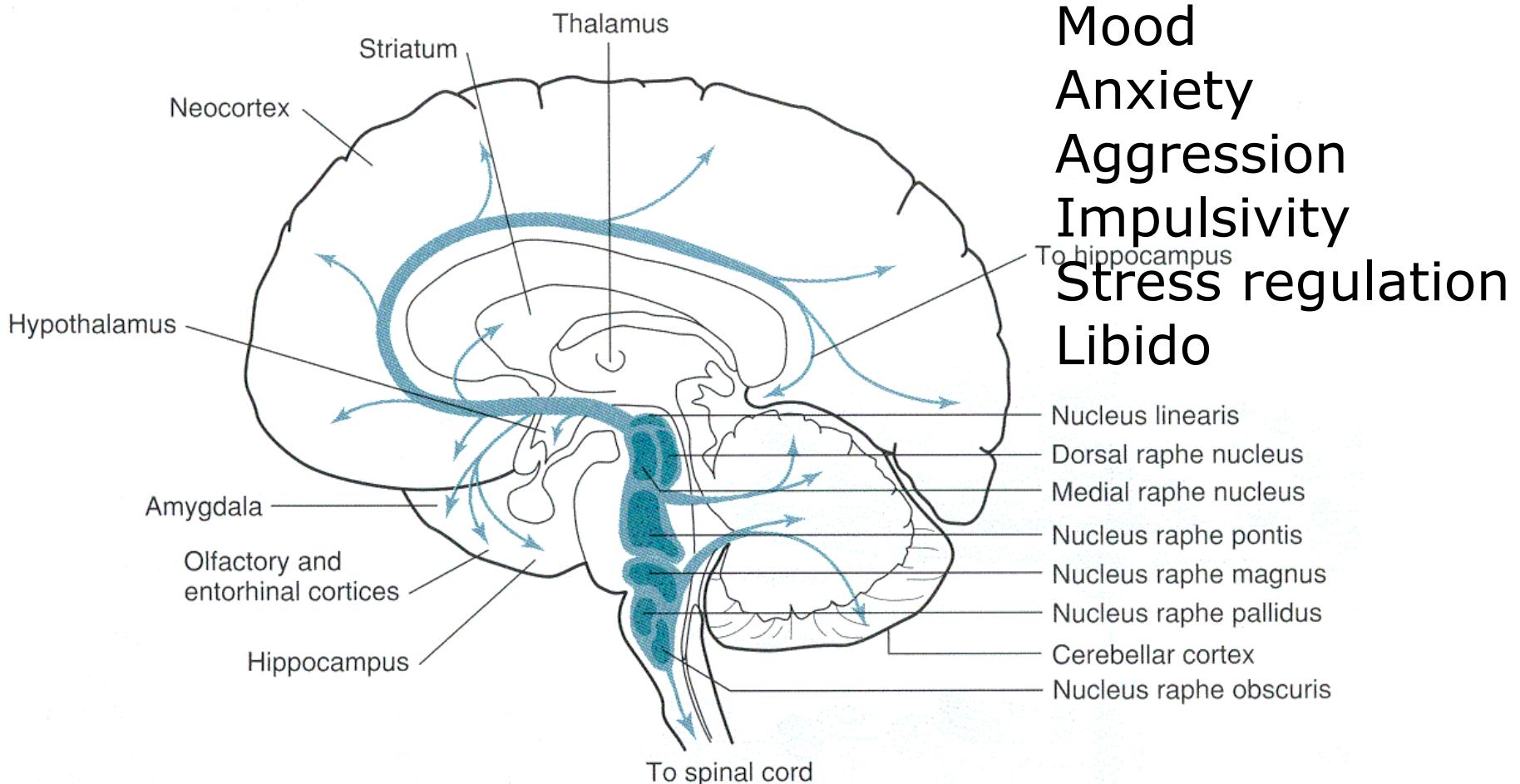


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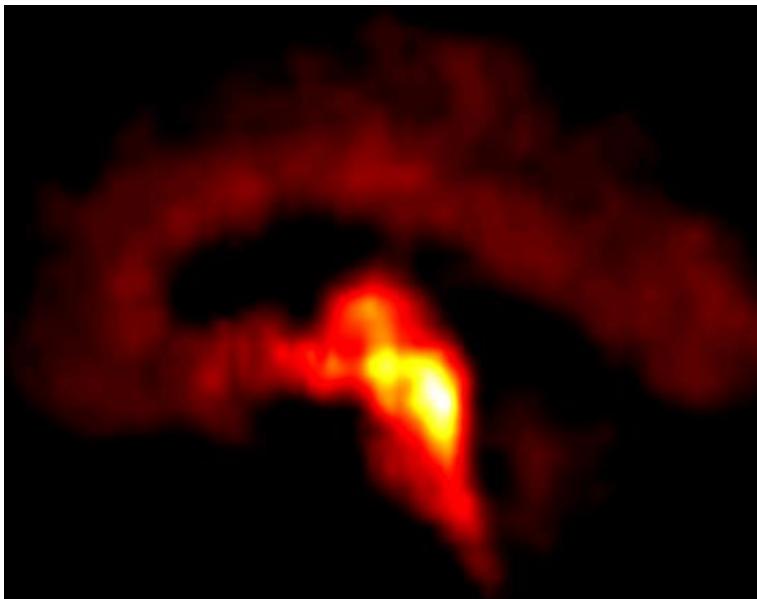
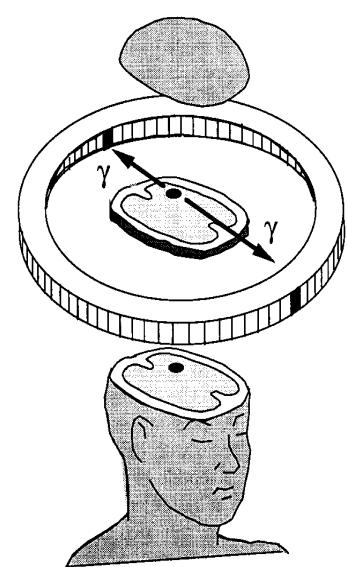
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Center for integrated
molecular brain imaging

Serotonerge nervebaner i hjernen



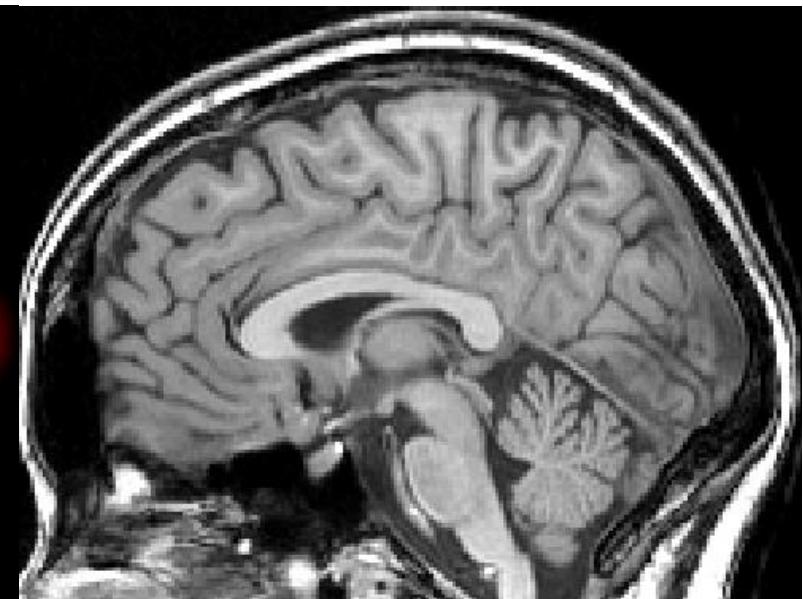
Raphe nuclei – kernen i serotonin system

PET imaging



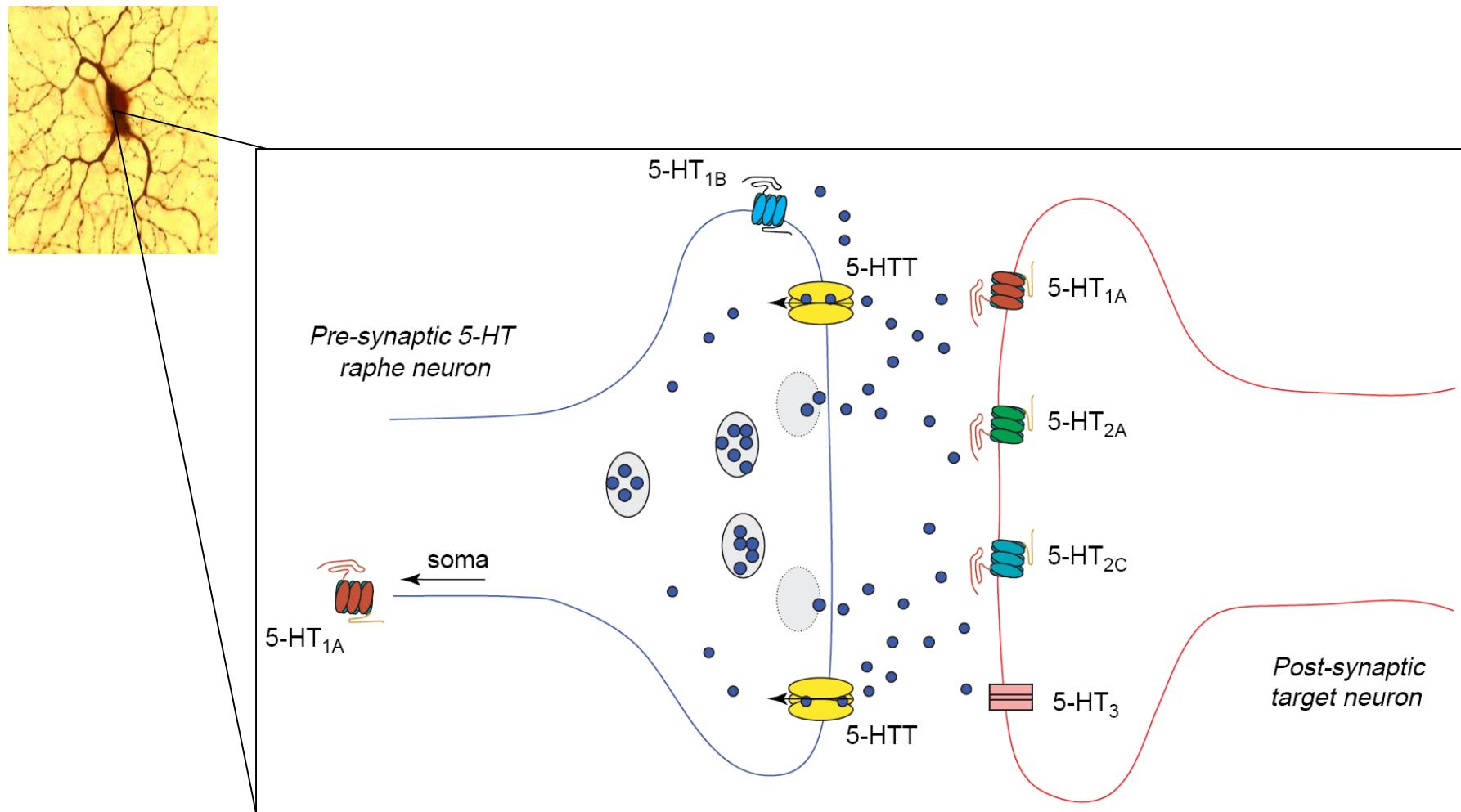
[¹¹C]DASB binds to serotonin transporter (5-HTT) and visualizes raphé nuclei

MRI 3T



No anatomical correlate on MR images

Serotonerg kommunikation via kemisk synapse



Hariri & Holmes, *TiCS* 2006

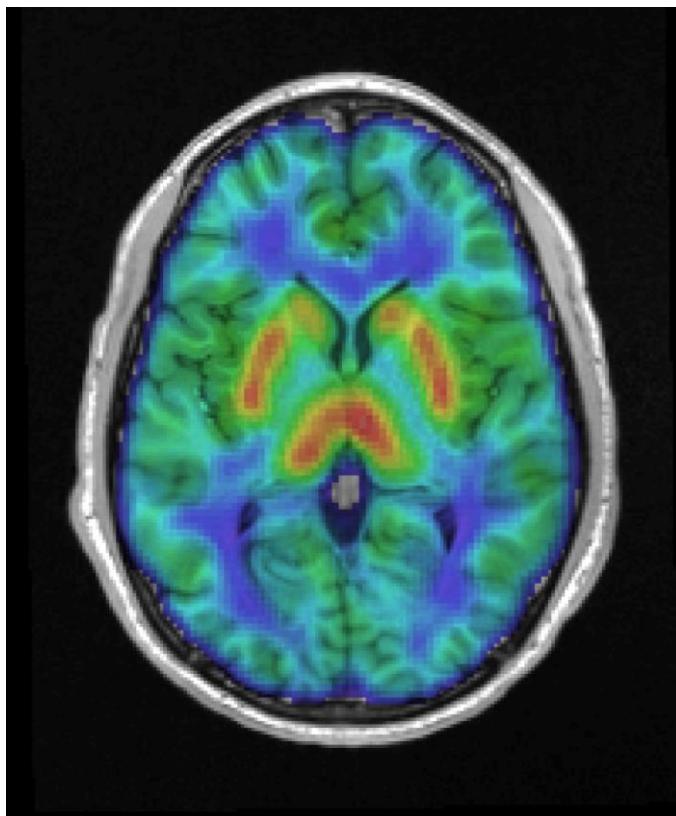


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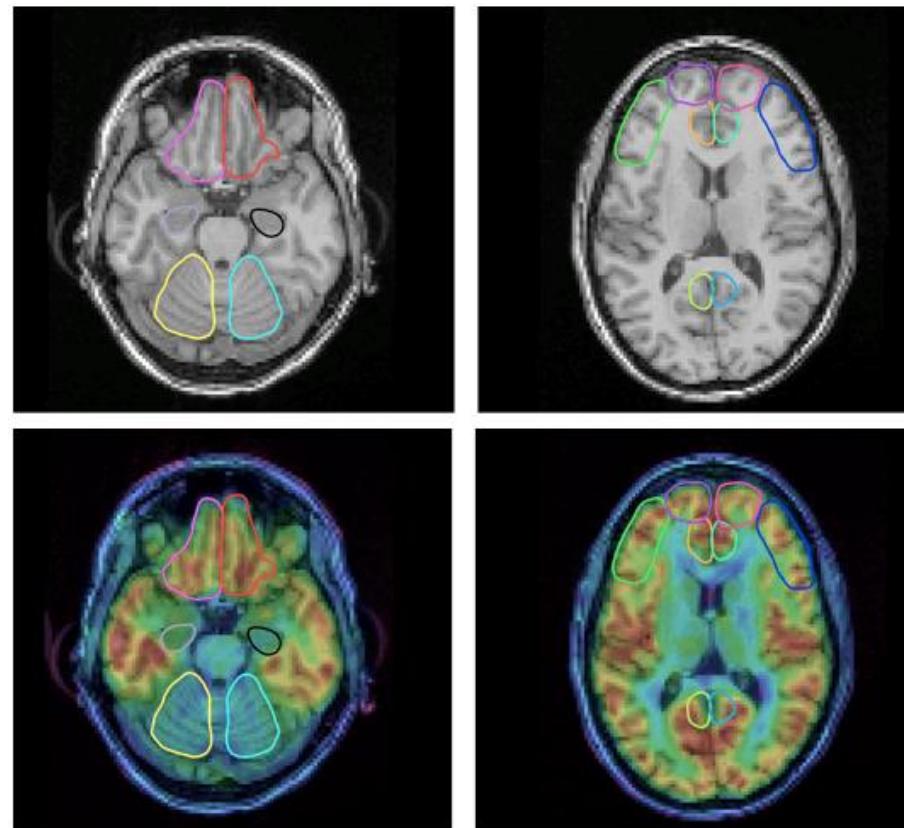
Hjernebilleder af serotonerge markører

Serotonin transporter



11C-DASB PET

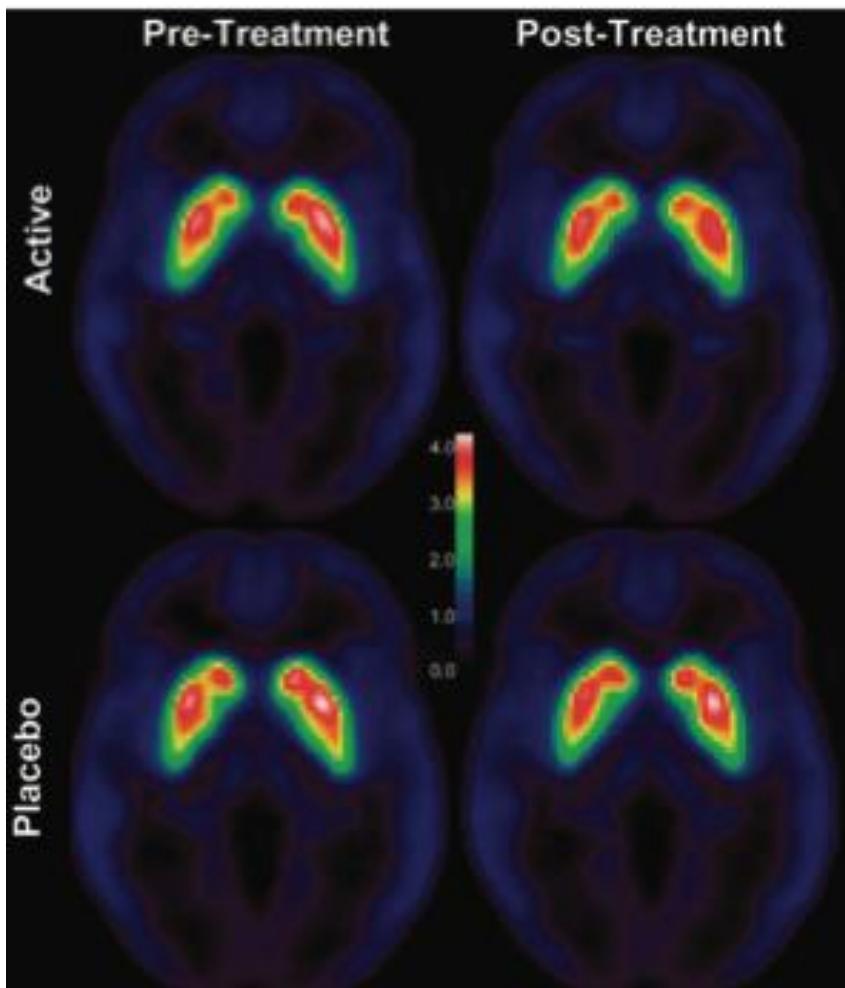
Serotonin 2A receptor



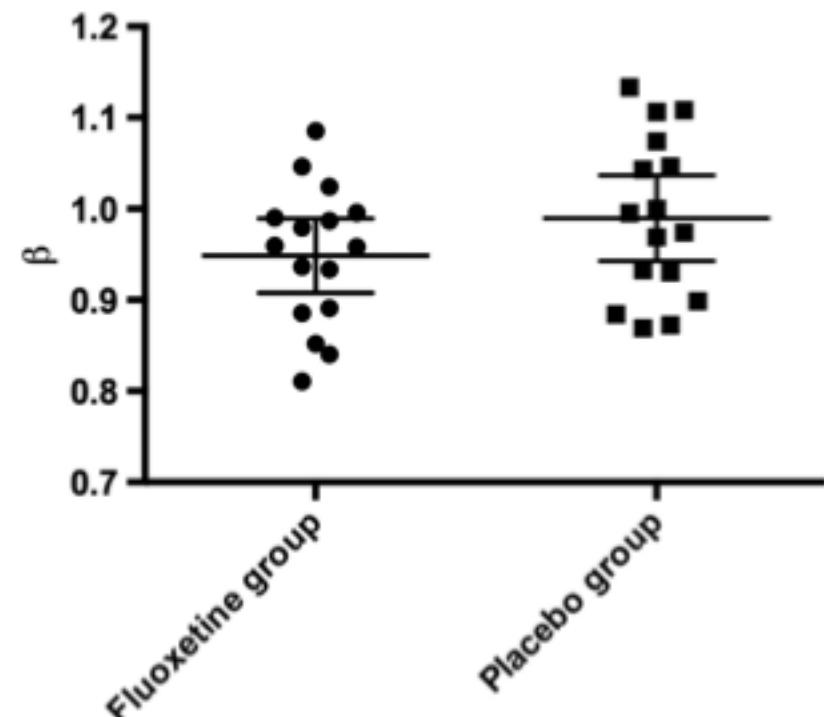
18F-Altanserin PET

Billeder af serotonin 4 modtageren – en markør for serotonin tonus?

[¹¹C-SB207145 PET – effects of 3 weeks SSRI



Baseline vs follow-up beta difference
– less binding at follow-up with 3 weeks SSRI



Haahr et al 2014

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1. Stresshormon-dynamik og serotonin

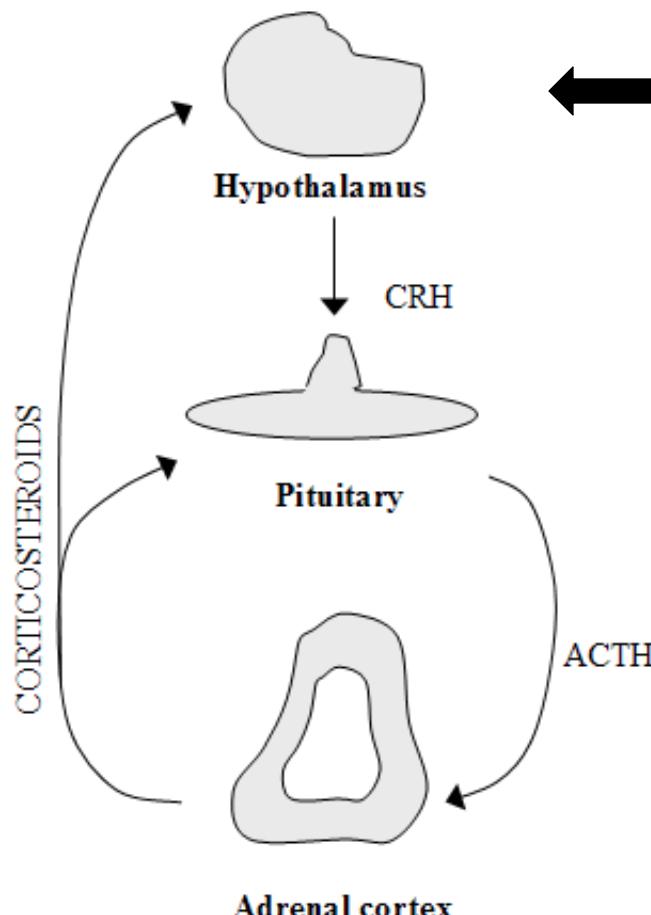
- Stress is implicated in pathophysiology of mood disorders
- Individuals at high familial risk for mood disorders show characteristic serotonin signaling signatures and stronger coupling to personality traits reflecting coping styles
Frokjaer2008, 2009, 2010
- Stress vulnerability and cortisol awakening response is linked to serotonergic neurotransmission on a genetic basis
Caspi2003, 2010, Uher2008, Gotlib2008, Vreeburg2010

**-> Støtter serotonin-systemet vores dynamisk stress-respons
som kan hjælpe os til at navigere sundt gennem
belastninger, knubs og kriser?**



Regulering af stresshormon (kortisol)

Hypothalamic-pituitary-adrenal (HPA) akse

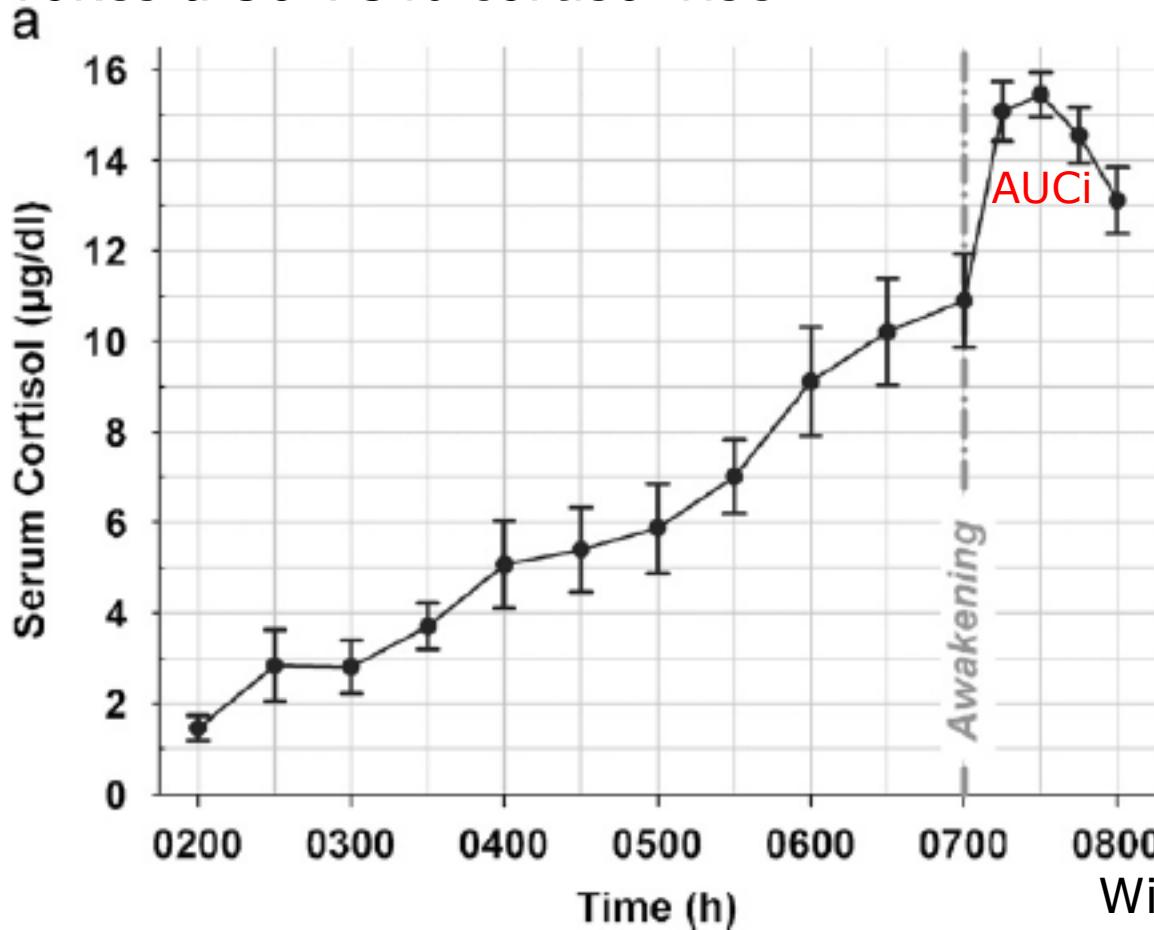


Lys-information
via øjet og suprachiasmic
nucleus

Genererer:
Døgnrytme
Respons på stress stimuli
Kortisol opvågningsresponset

Kortisol opvågningsresponset som et mål for kortisoldynamikken

Awakening is a potent stimulus of the HPA-axis and provokes a 50-75% cortisol rise



Wilhelm 2007



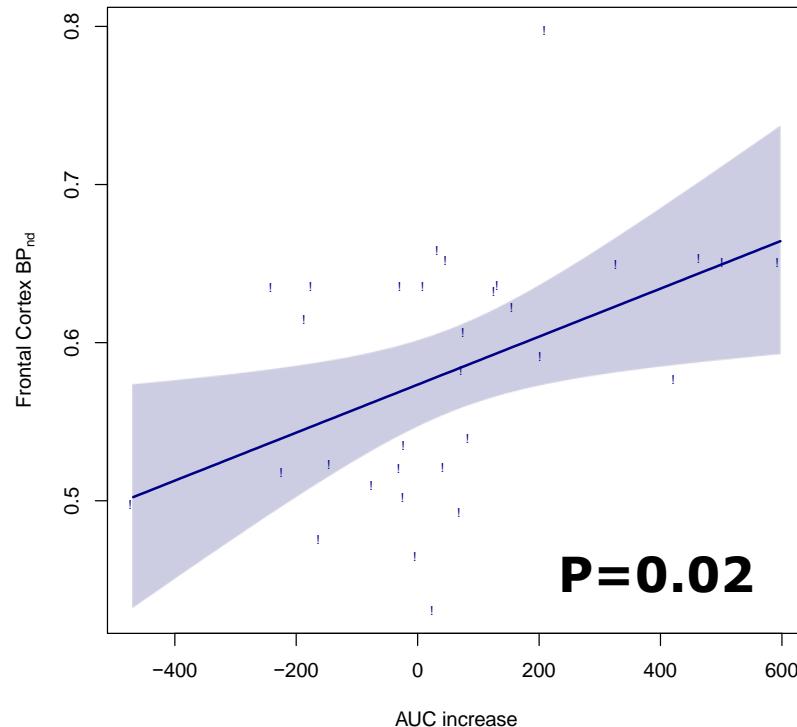
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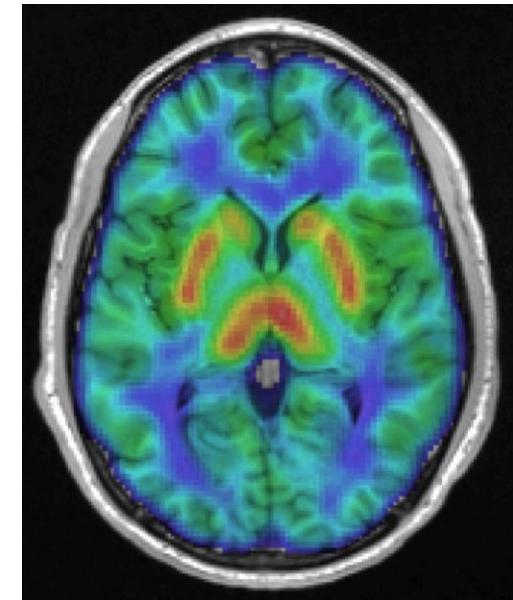
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1. Serotonin bremsemolekyle og kortisol opvågningsresponset hos raske

Prefrontal serotonin transporter og kortisol opvågningsresponses



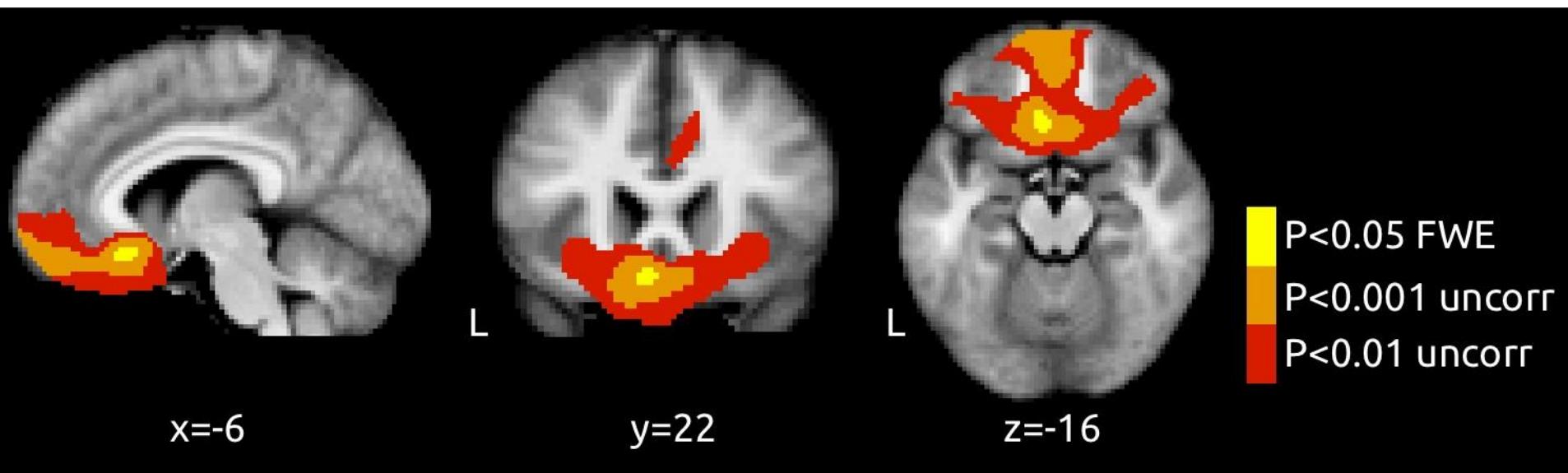
Anterior cingulate: $p=0.06$



N=32, 7 women
Age: 35.3 (19.7-81.7)
42% L_A/L_A 5-HTTLPR

1. Serotonin bremsemolekyle og kortisol opvågningsresponset hos raske

1. FWE correction ($p<0.05$), significant cluster in left ventromedial prefrontal cortex
2. Uncorrected $p<0.05$, brain mask $BP_{ND}>0.1$, support prefrontal association

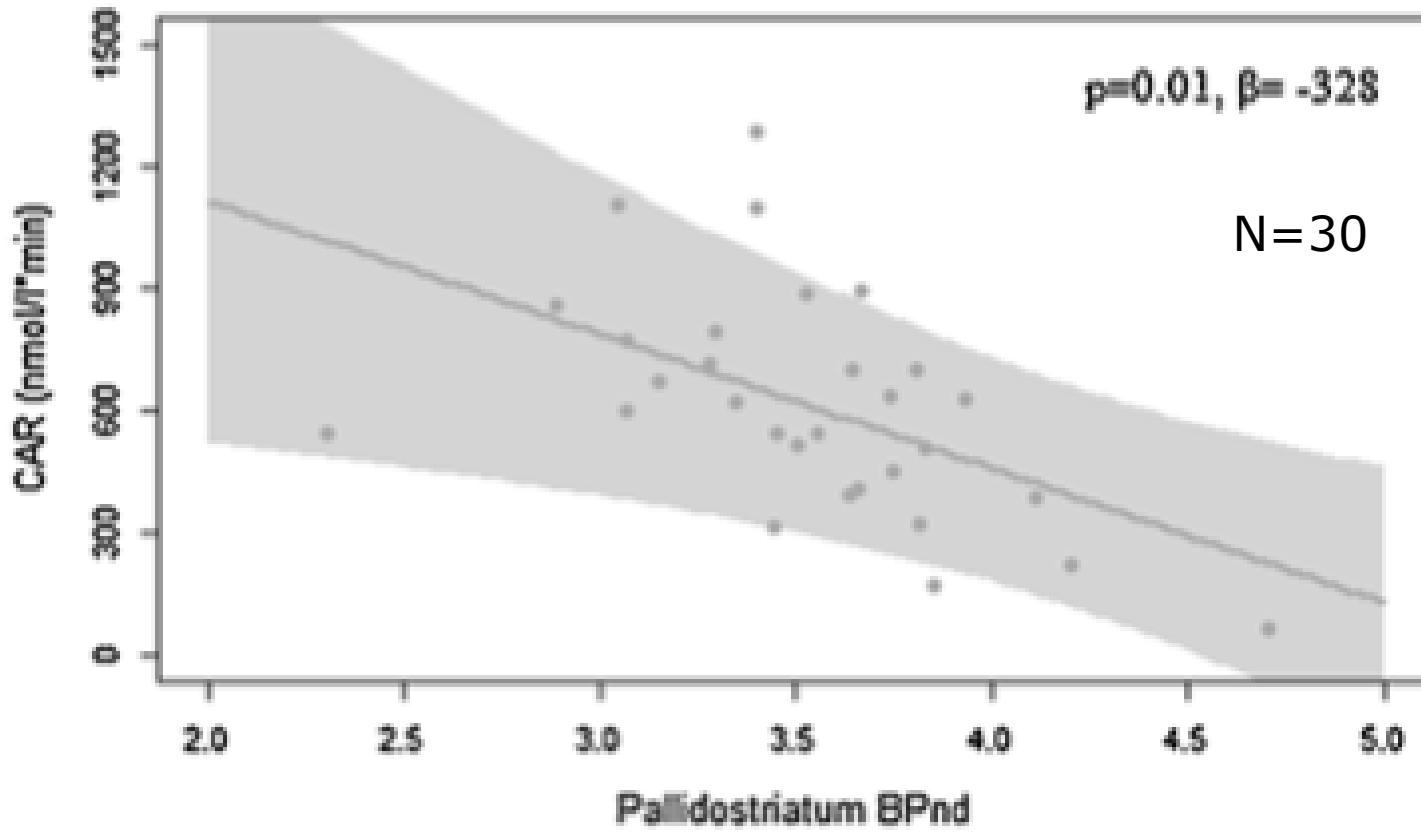


$N=26 (<40$ years), age adjusted

Frokjaer et al 2013, replicated Frokjaer 2014



1. Kortisol opvågningsresponset og serotonin tonus (serotonin 4 receptor som proxy)



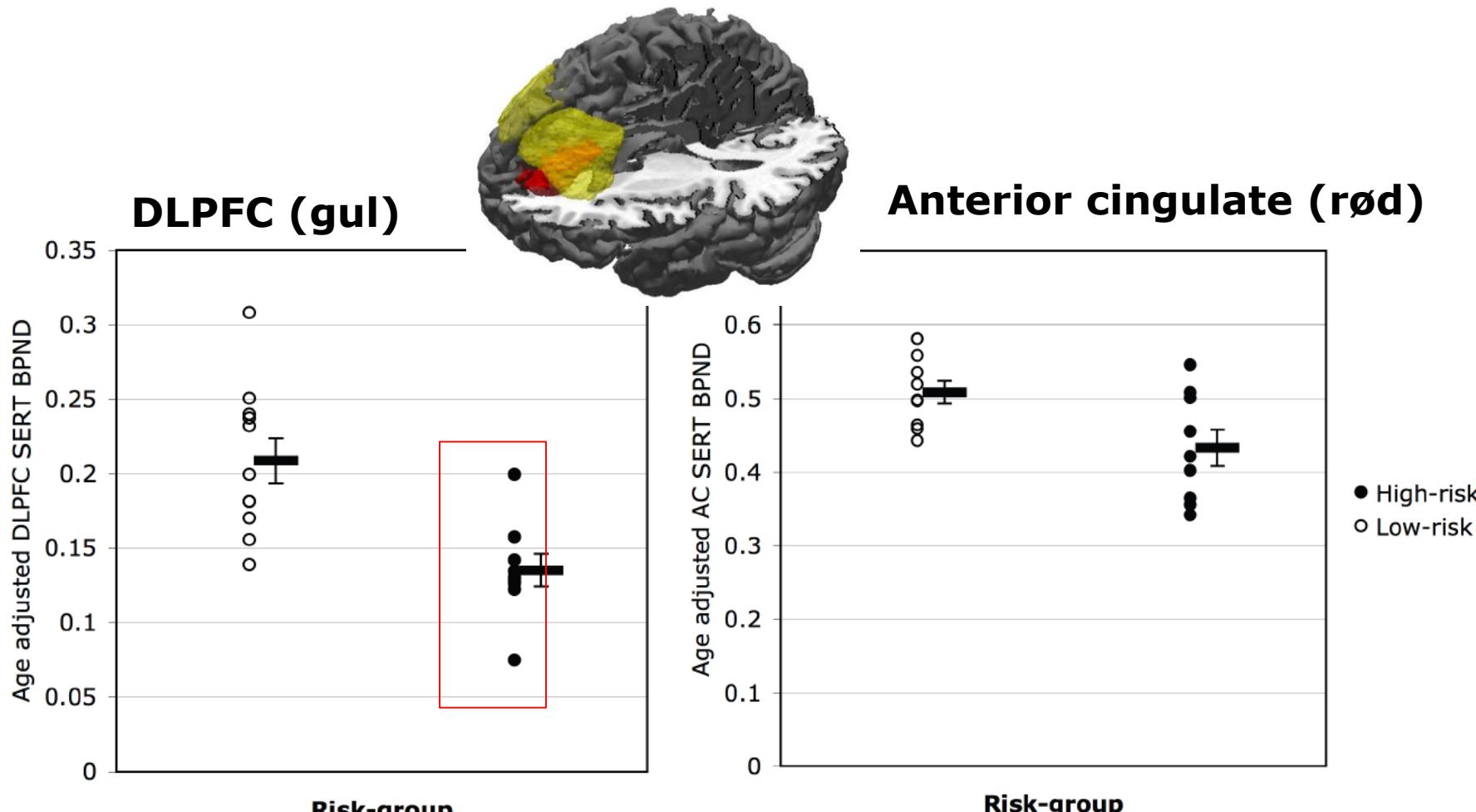
Jakobsen, Frokjaer Psychoneuroendocrinology 2016



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NRU, Copenhagen University Hospital, Rigshospitalet

2. Familiær risiko for depression og serotonin bremsemolekylet – kompensatorisk nedreguleret?



Frokjaer et al 2009



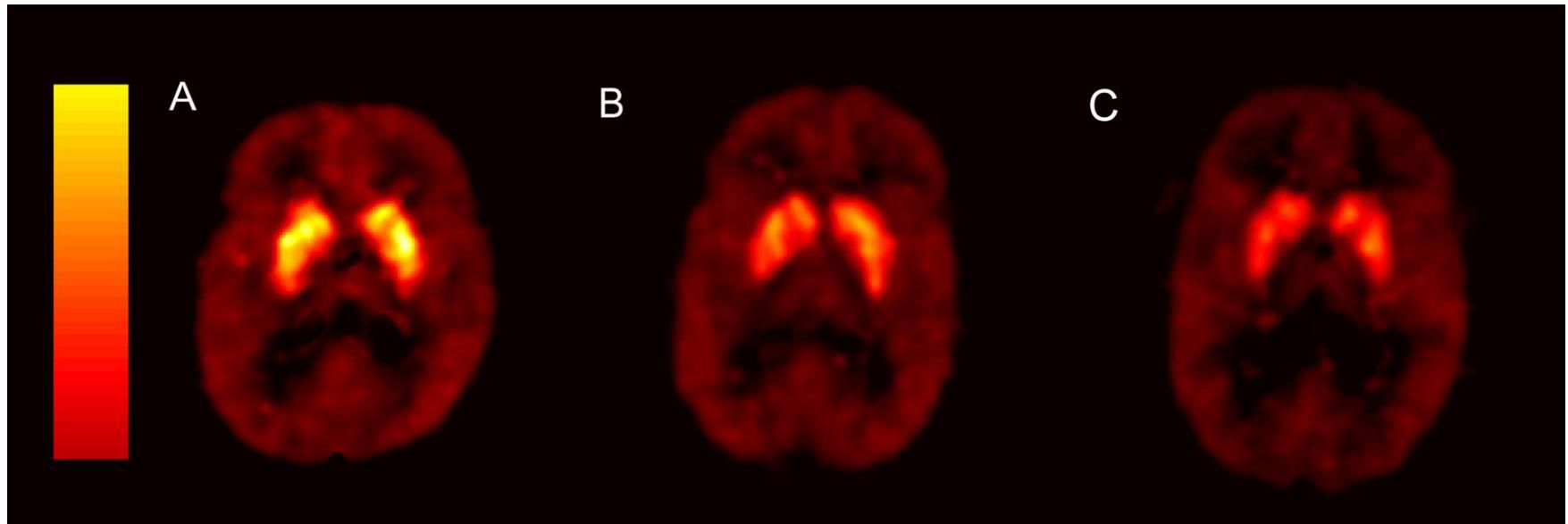
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2. Sænkes serotonin tonus kompensatorisk ved øget genetisk risiko for depression?

[¹¹C]SB207145 binding potentials

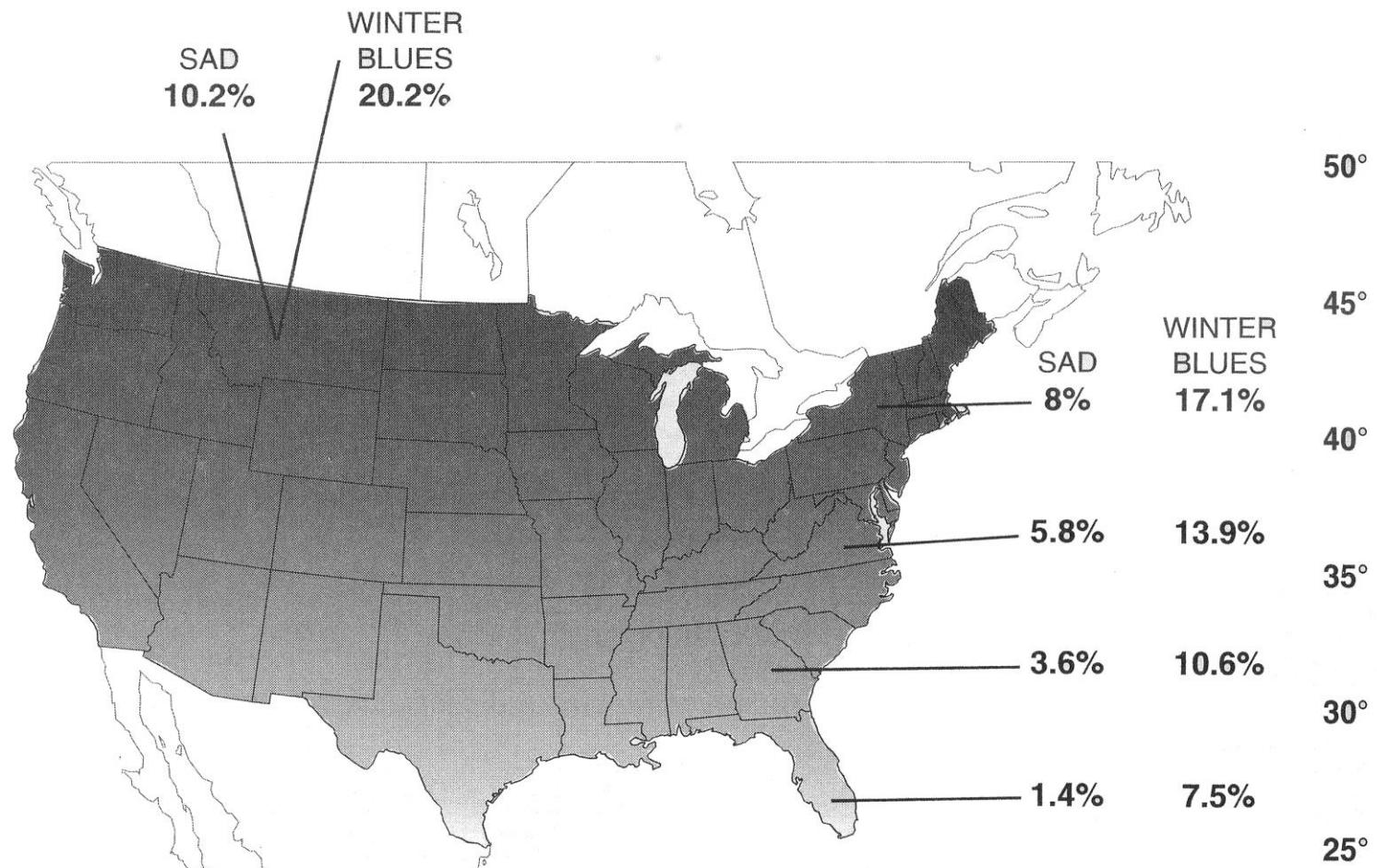


of MDD-relatives → → →

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Madsen, Frokjaer et al 2014

3. Årstider og depression: spiller serotonin en rolle?



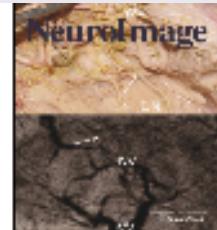
PET population – Cimbi database ressource



Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimng



The Center for Integrated Molecular Brain Imaging (Cimbi) database

Gitte M. Knudsen^{a,b,i,*}, Peter S. Jensen^{a,b}, David Erritzoe^{a,b}, William F.C. Baaré^{a,c}, Anders Ettrup^{a,b}, Patrick M. Fisher^{a,b}, Nic Gillings^{a,d}, Hanne D. Hansen^{a,b}, Lars Kai Hansen^{a,e}, Steen G. Hasselbalch^{a,b,i}, Susanne Hennigsson^{a,c}, Matthias M. Herth^{a,b,d,f}, Klaus K. Holst^{a,b,g}, Pernille Iversen^{a,c}, Lars V. Kessing^{h,i}, Julian Macoveanu^{a,c,h}, Kathrine Skak Madsen^{a,c}, Erik L. Mortensen^{j,i}, Finn Årup Nielsen^{a,e}, Olaf B. Paulson^{a,b,c,i}, Hartwig R. Siebner^{a,c,i,k}, Dea S. Stenbæk^{a,b}, Claus Svarer^{a,b}, Terry L. Jernigan^l, Stephen C. Strother^{m,n}, Vibe G. Frokjaer^{a,b,h}

*The Cimbi database currently comprises a total of **1100 PET and 1000 structural and functional MRI scans** and it holds a multitude of additional data, such as genetic and biochemical data, and scores from 17 self-reported questionnaires and from 11 neuropsychological paper/computer tests. The database associated Cimbi biobank currently contains blood and in some instances saliva samples from about **500 healthy volunteers and 300 patients** with e.g., major depression, dementia, substance abuse, obesity, and impulsive aggression. Data continue to be added to the Cimbi database and biobank.*

Knudsen et al 2016

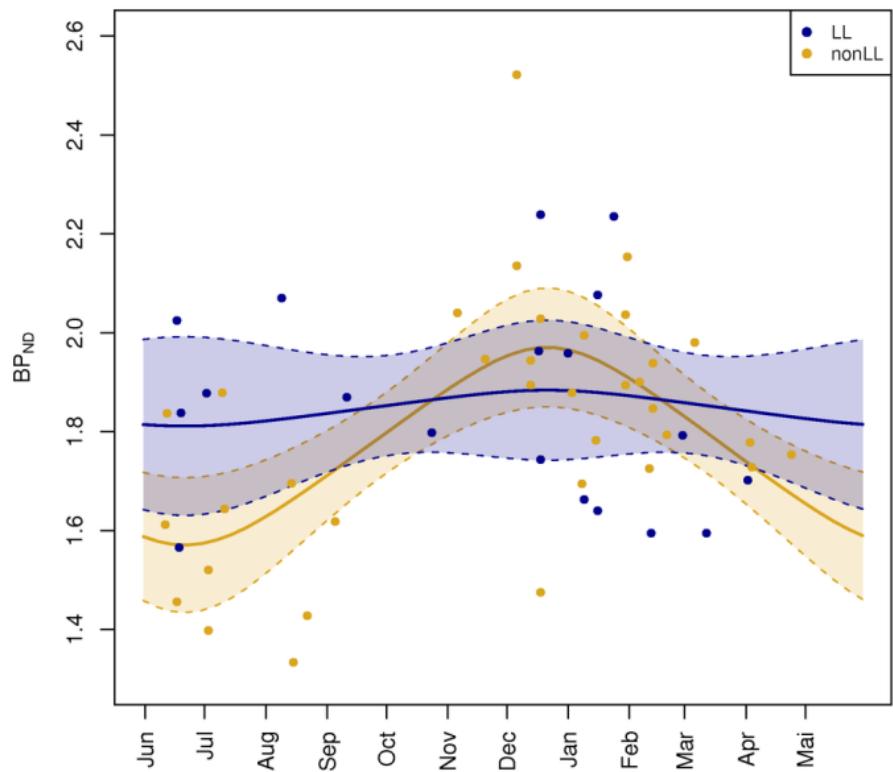
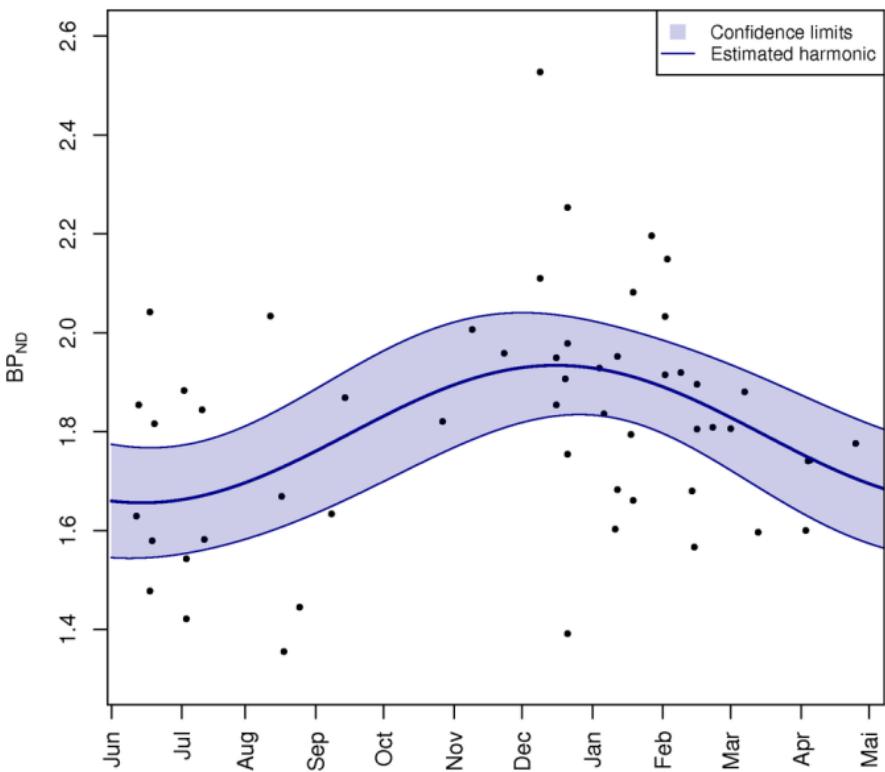


Vibe G. Frokjaer

NRU, Copenhagen University Hospital, Rigshospitalet

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3. Årstd og serotonin – raske hjerner

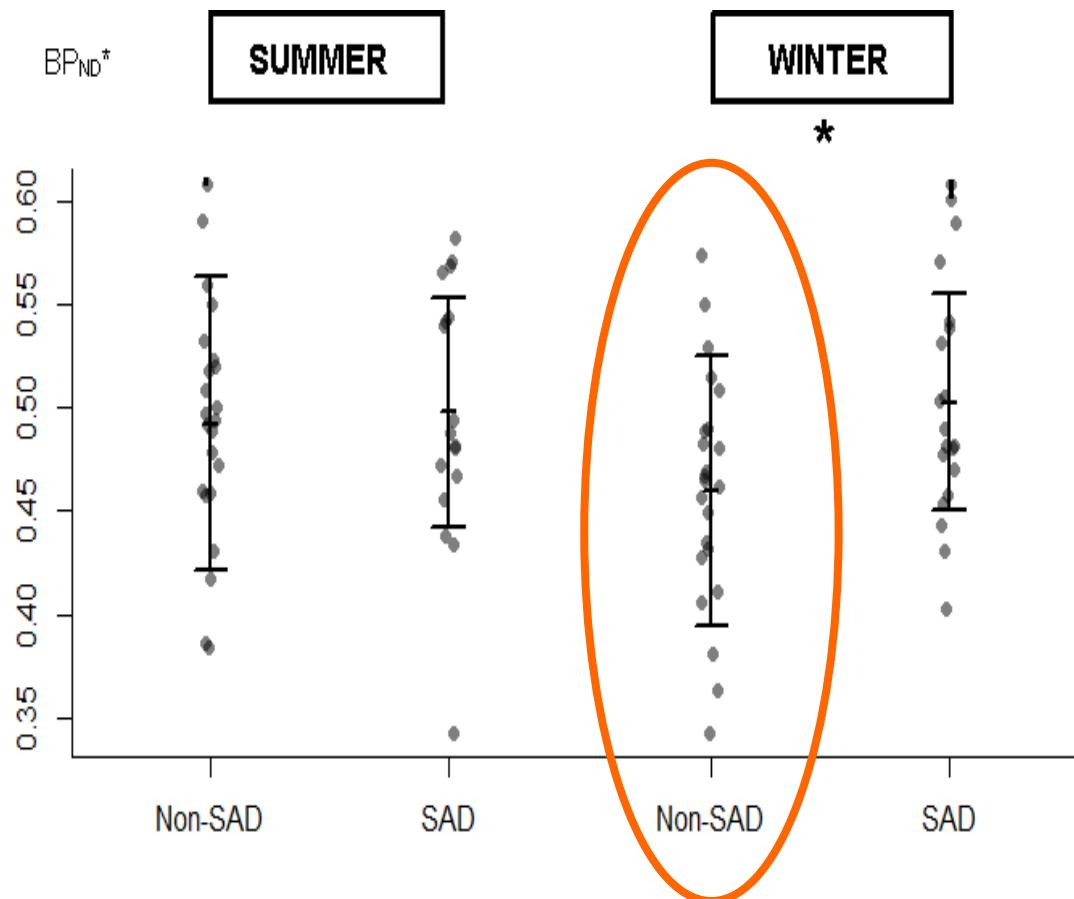


Genotype X season interaction

Kalbitzer *et al.* 2010



3. Mangel på kompensation -> vinter depression?



McMahon et al. Brain 2016, 2018



Opsamling

Hos raske mennesker er kortisol opvågningsresponset koblet til markører for hjernens serotonininsystem

Serotonininsystemet kan støtte et dynamisk og veltilpasset stresshormonrespons hos raske mennesker

Adaptive (ikke-farmakologiske) hjerneændringer som øger serotonin tonus kan være en relevant kompensatorisk mekanisme ved belastninger eller høj risiko for depression
– fx familiær risiko

-> Serotonin støtter sund stresshåndtering?



Diskussion og perspektiver

Dynamikken i fokus

Psykoedukation

Afstigmatisering

Monitorere forebyggende indsatser eller behandlinger?



Vibe G. Frokjaer

NRU, Copenhagen University Hospital, Rigshospitalet



Tak



And thanks to: project participants, PET and MRI staff, MR-assistants, Lab-staff, Students, Database coordinator, Collaborators, Funding, Others

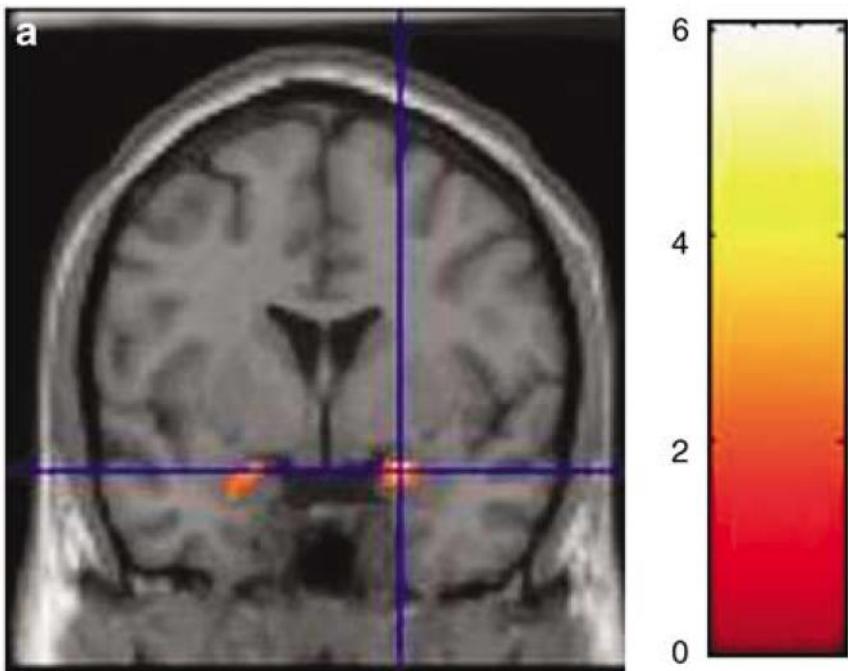


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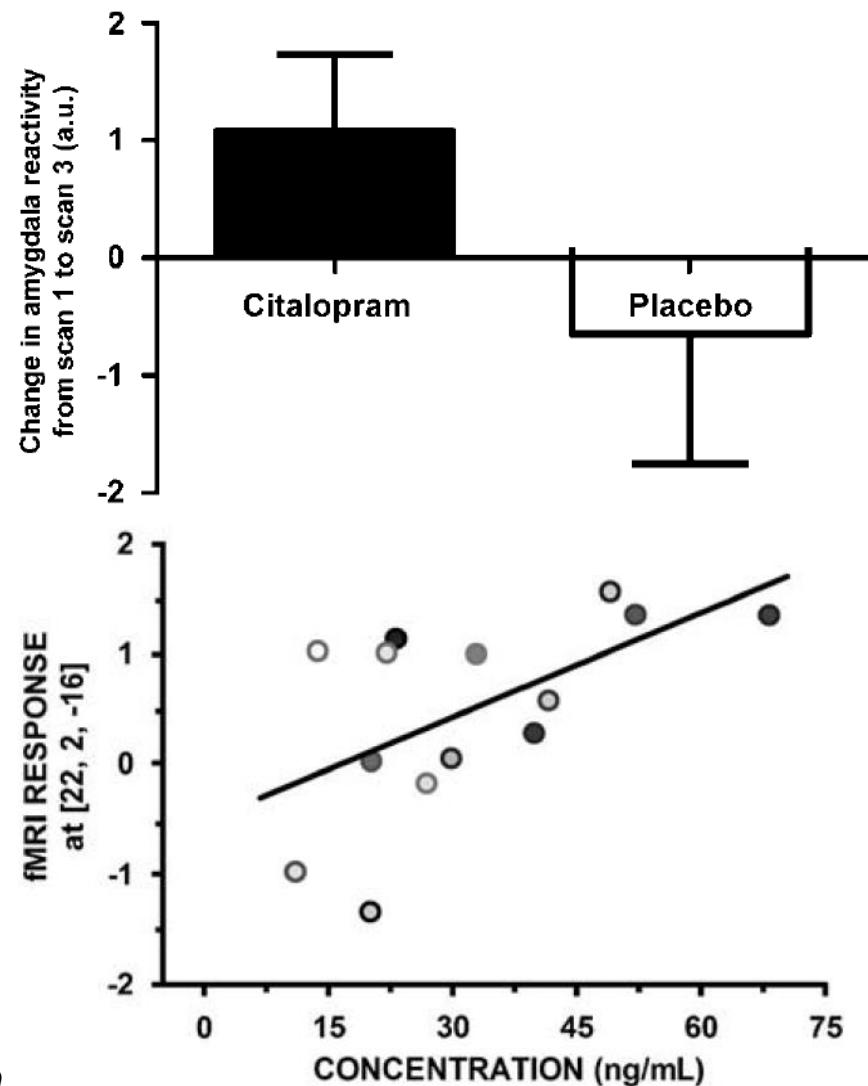
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Acute increase in amygdala response

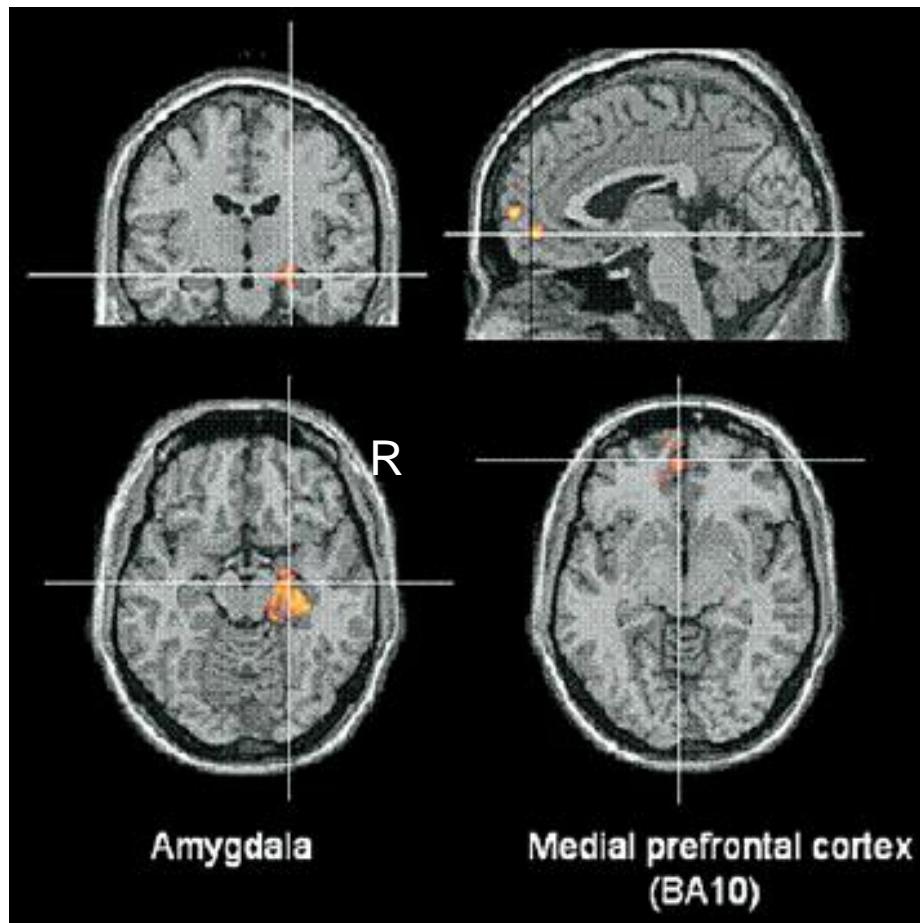


20 mg citalopram (or placebo) administered intravenously over 30 minutes

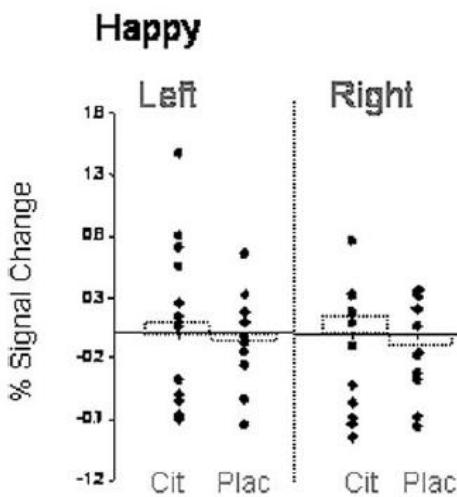
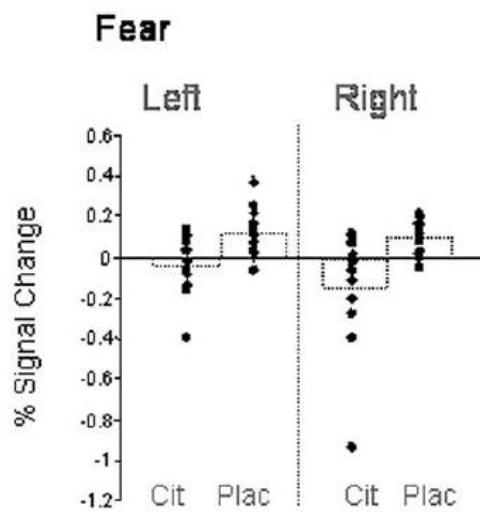
Rescan coincided with end of administration



7-day oral protocol and lower amygdala response



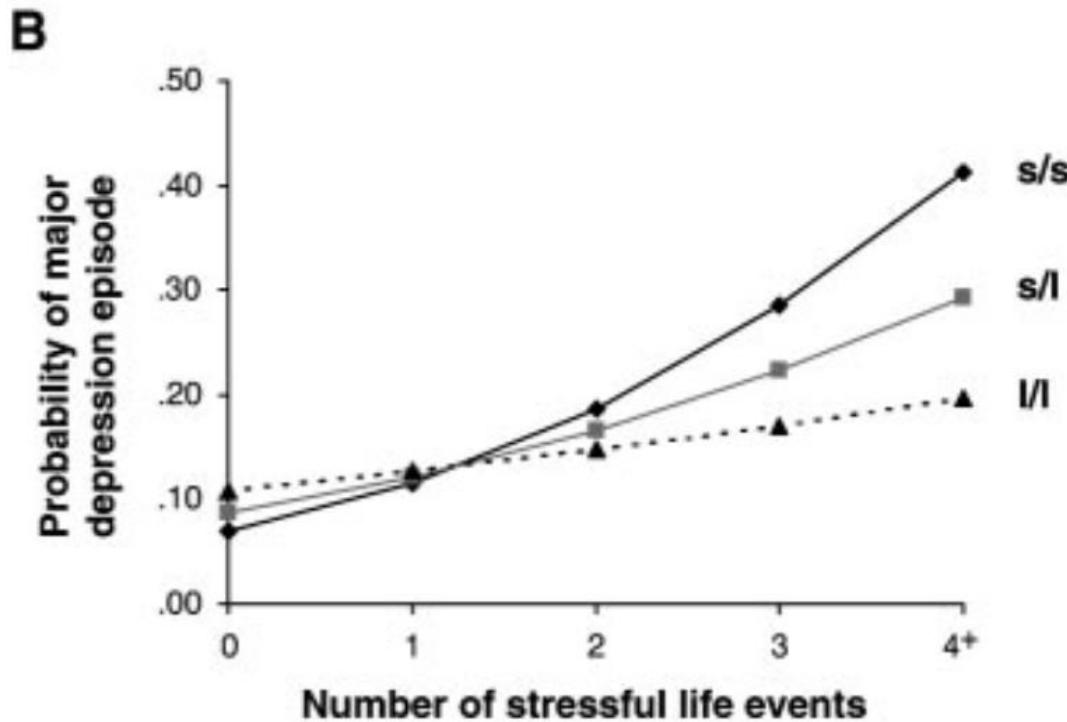
20 mg citalopram (or placebo) administered orally each day for 7 days



Gen X miljø effekter: Stress sårbarhed og genetiske varianter

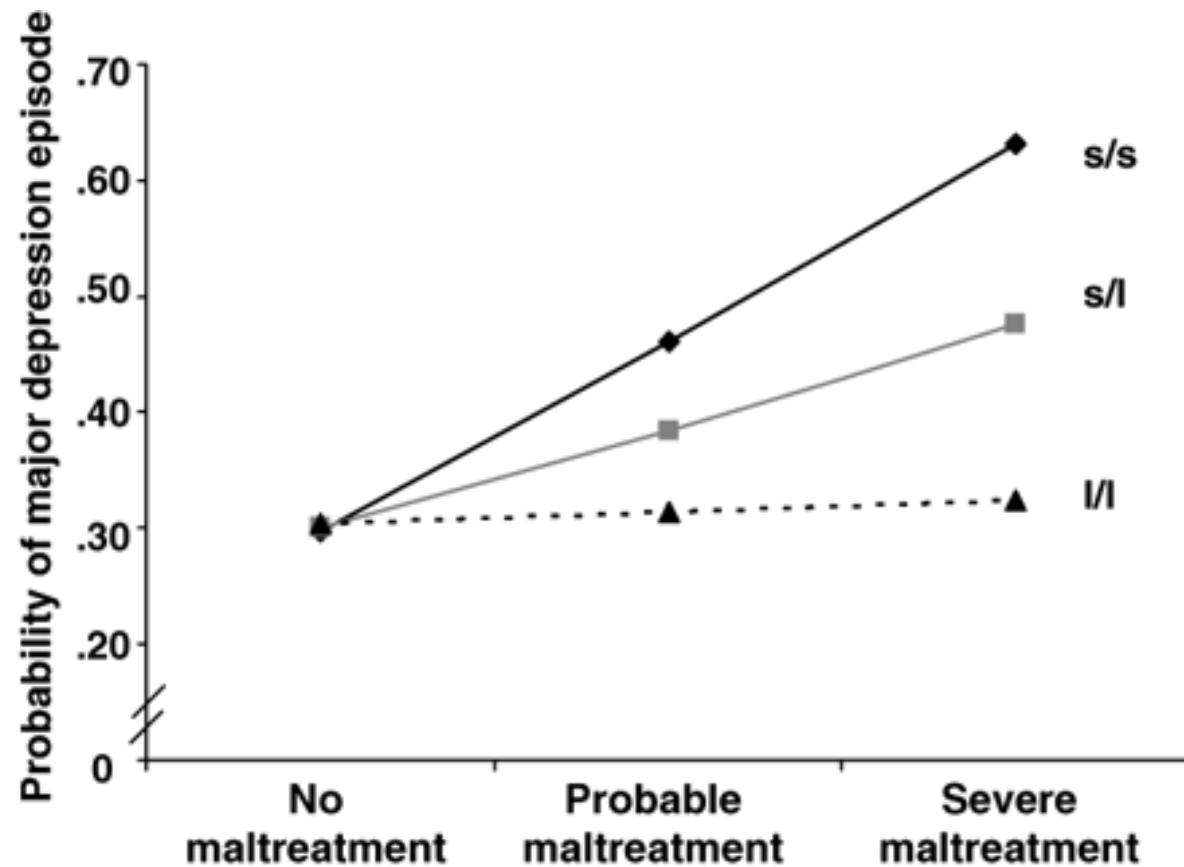
N= 1037, NZ birth cohort. 96% follow-up at 26 years

Outcome measures: SLE 5 years before, past year depression



Caspi et al 2003

5-HTLPR x omsorgssvigt og risiko for depression



Personligheds mål (NEO-PI-R)

- Based on a questionnaire with 240 self-reported answers
- Model operating with five basic personality dimensions based on 30 personality traits
- Dimensions include
 - **Neuroticism**
 - Extraversion
 - Agreeableness
 - Conscientiousness
 - Openness

Costa & McCrae 1992



Personligheds-riskfaktor – coping index?

Personality measure (NEO-PI-R)

Examples of statements for Neuroticism assessment

“I can handle myself pretty well in a crisis”

“I often feel helpless and want someone else to solve my problems”

“It’s often hard for me to make up my mind”

“I often worry about things that might go wrong”

“I’m seldom apprehensive about the future”

“I rarely feel lonely or blue”

NEO-PI-R manual (Costa and McCrae 1992)

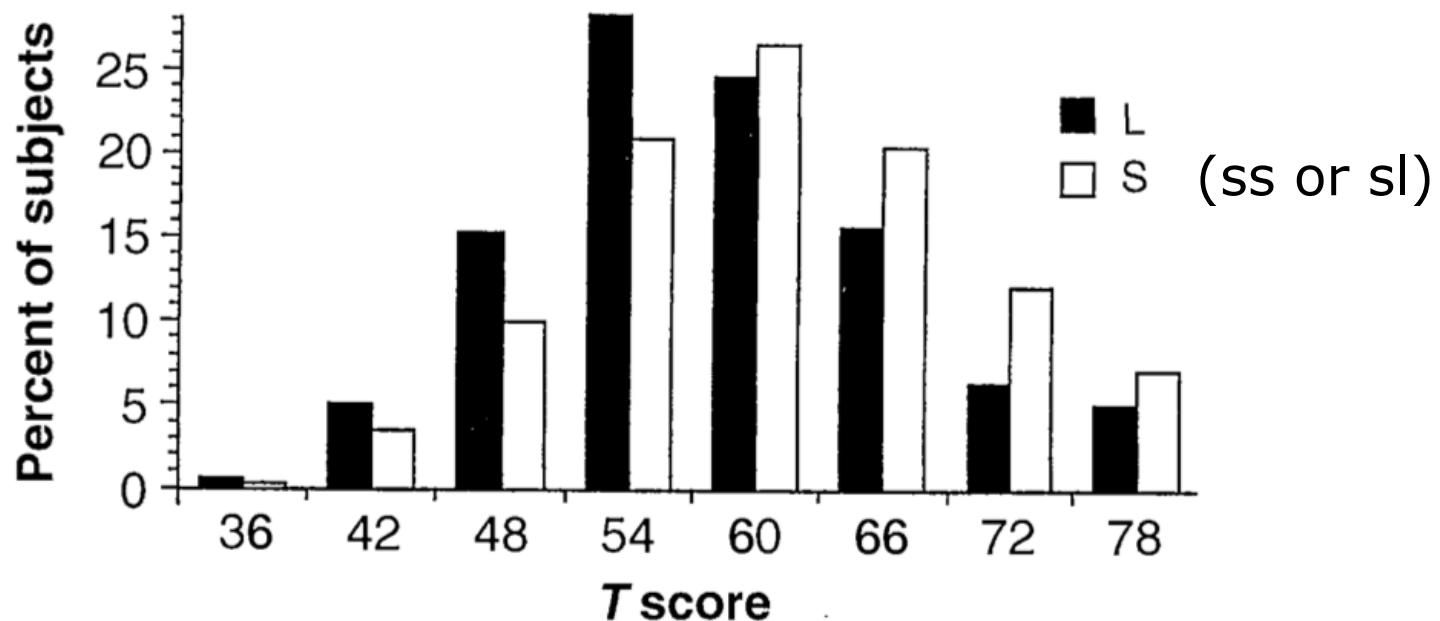


Neuroticisme og genetiske varianter af SERT

N=505

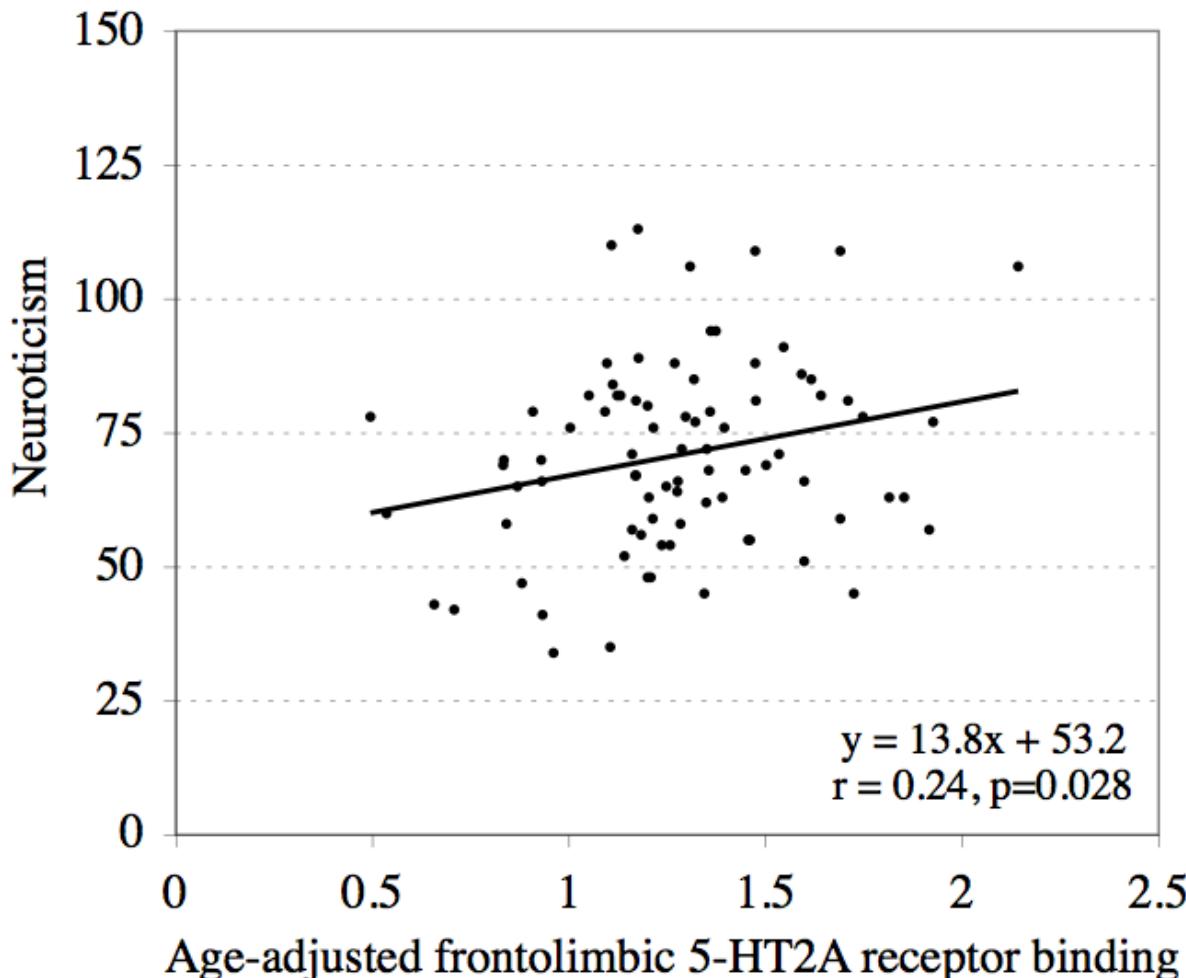
7-9% of inherited variance in personality traits

S-L: 3.4 T score value, p=0.002



Lesch et al 1996

Frontal serotonin 2A receptors and personligheds-risikofaktorer



Design

N=83

Healthy volunteers

52 males/ 31 females

Mean age: 43 (18-76)

Frokjaer et al 2008, Biol Psy

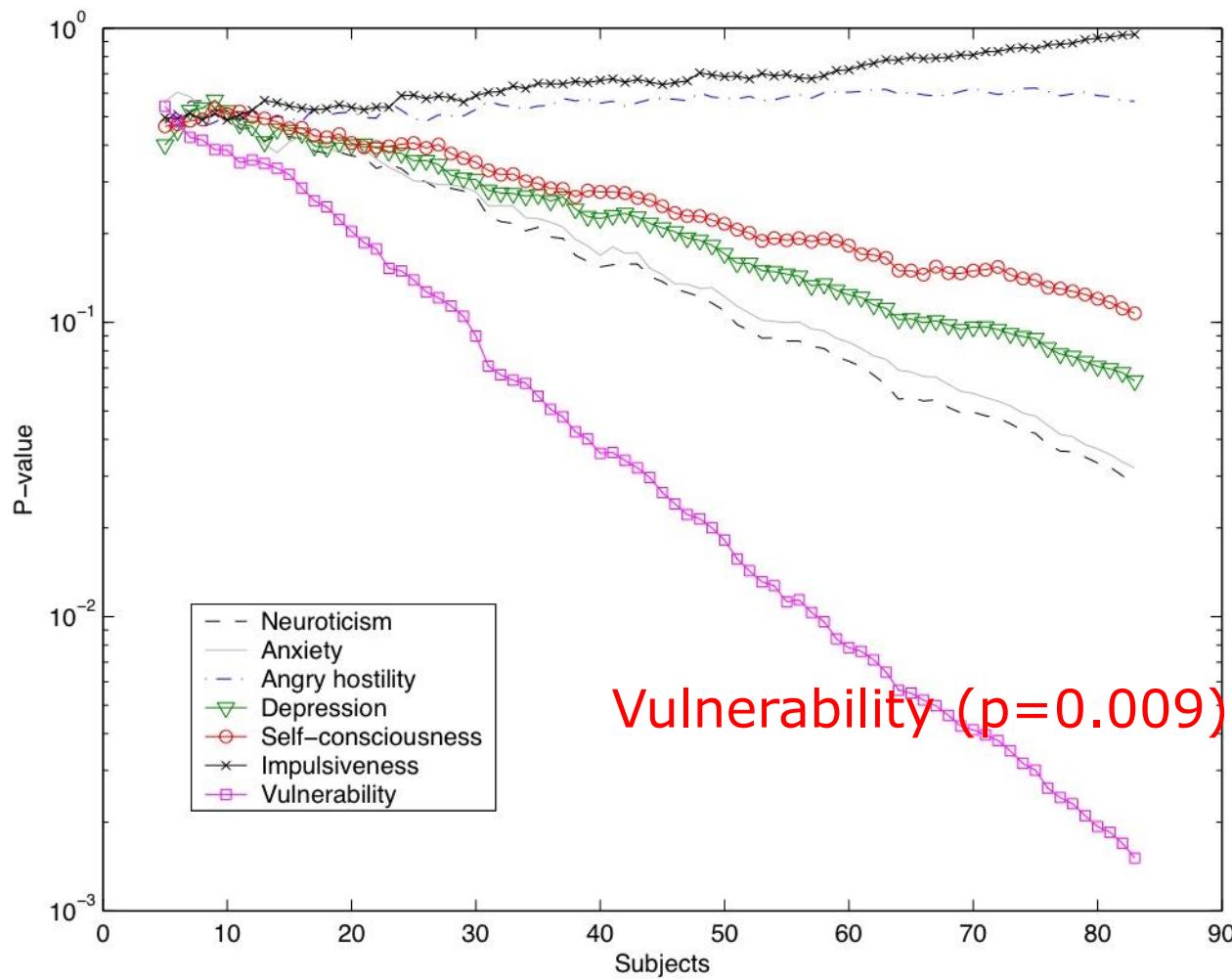


Vibe G. Frokjaer

NRU, Copenhagen University Hospital, Rigshospitalet

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Frontal serotonin 2A receptors and personligheds-risikofaktorer



Frokjaer et al 2008, Biol Psy



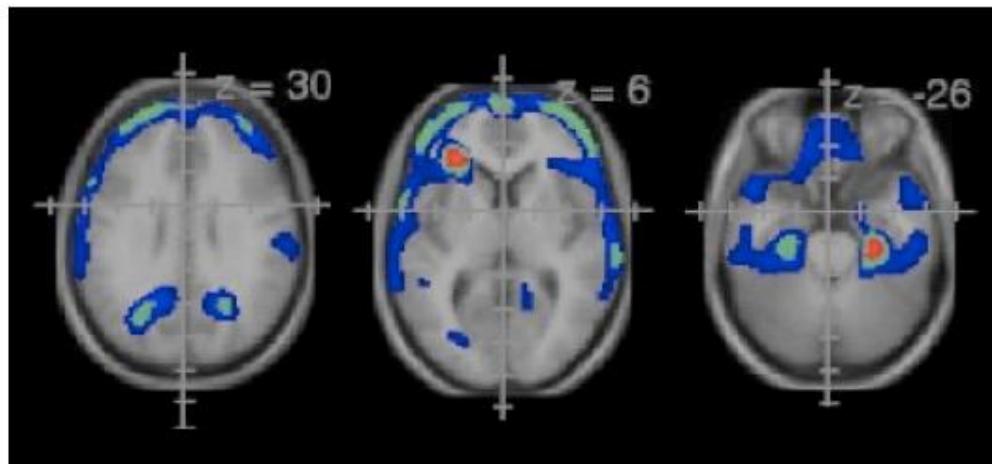
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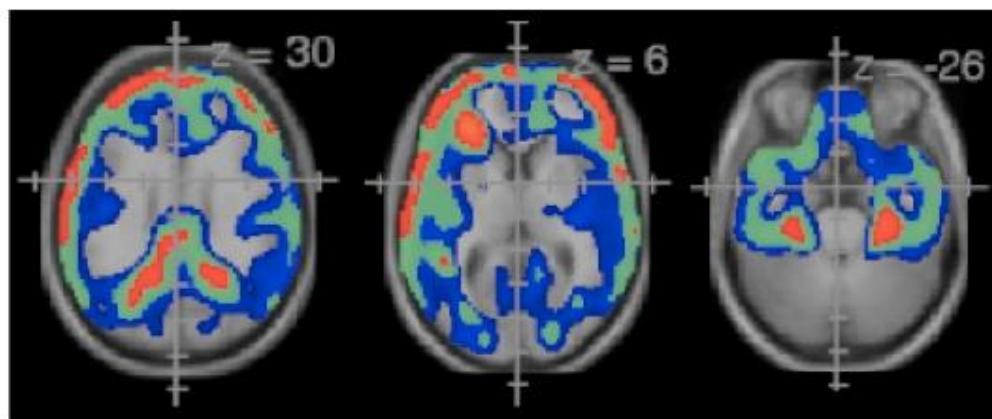
Neuroticism og serotonin 2A - mønster

a. Neuroticism

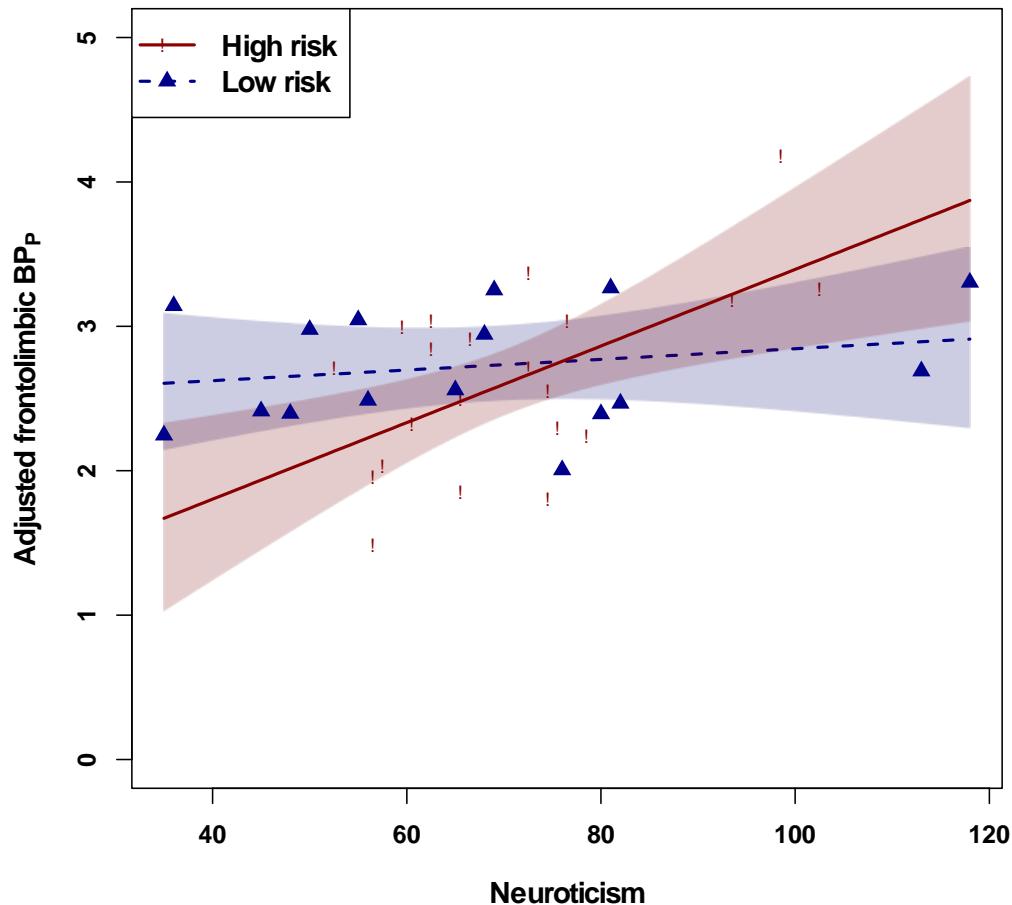


Red: p<0.001
Green: p<0.01
Blue: p<0.05

b. Vulnerability



Frontal serotonin 2A, neuroticisme og familiær risiko



N=37, 21HR, 16LR

Uni/bipolar: 17/4
Age: 39.3/38.6

High-risk: p=0.0037
Low-risk: p=0.52

Difference in slope:
p=0.026

(adjusted for BMI (p=0.008)
and age (p=0.03))

Frokjaer et al, 2010 Neuropsychopharmacology



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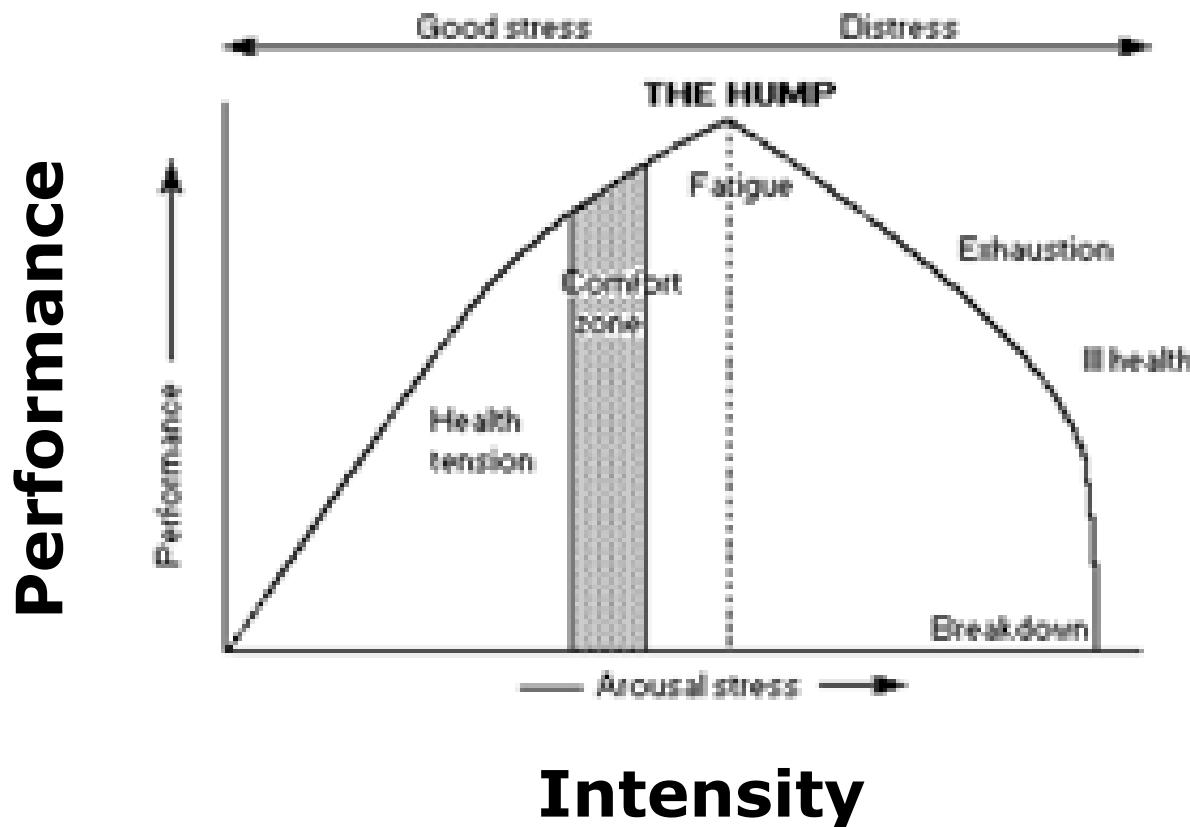
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Stress definition – godt eller skidt?

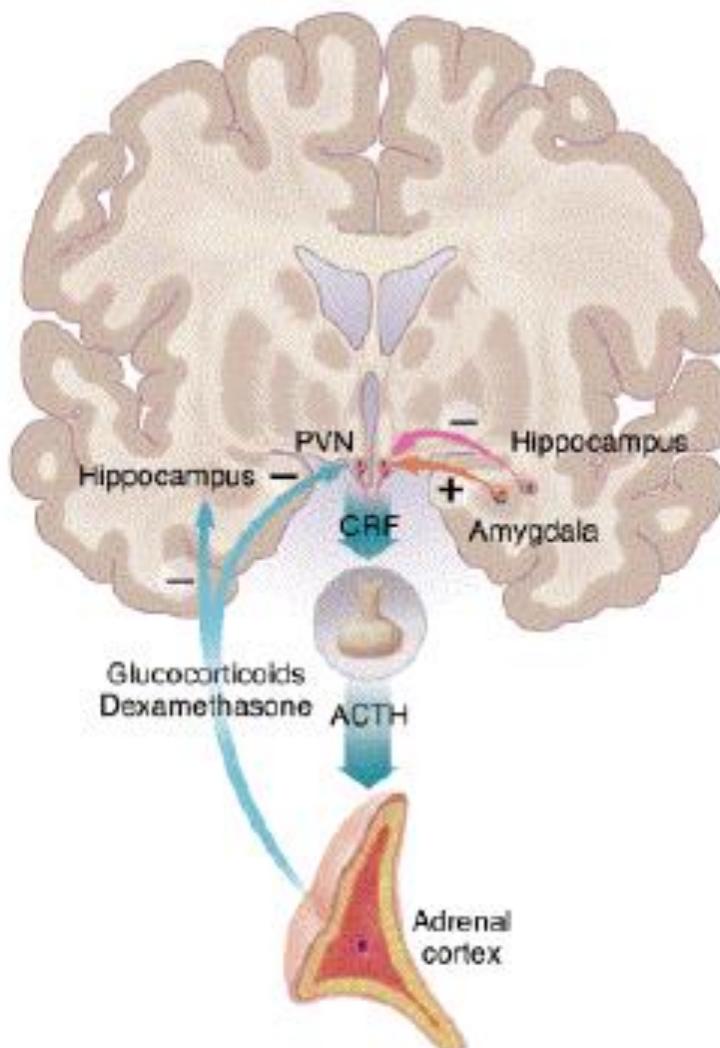
Hans Selye 1936:

"the non-specific response of the body to any demand for change"



Stress biology

The hypothalamic-pituitary-adrenal (HPA) axis

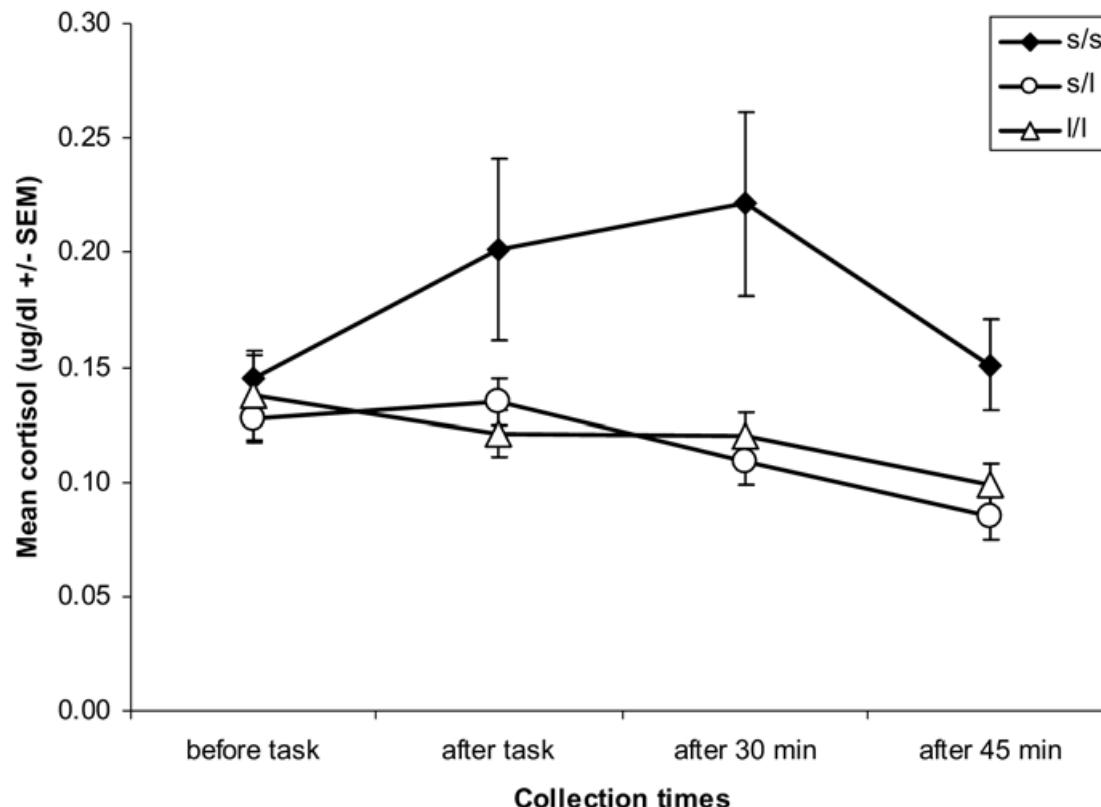


+Suprachiasmatic nucleus (SCN), sensitive to light, (biological clock) projects to PVN, and also via autonomic projections sets the ACTH sensitivity of the adrenal gland

Generates:
Circadian rhythm
Responses to stress stimuli
Cortisol awakening response



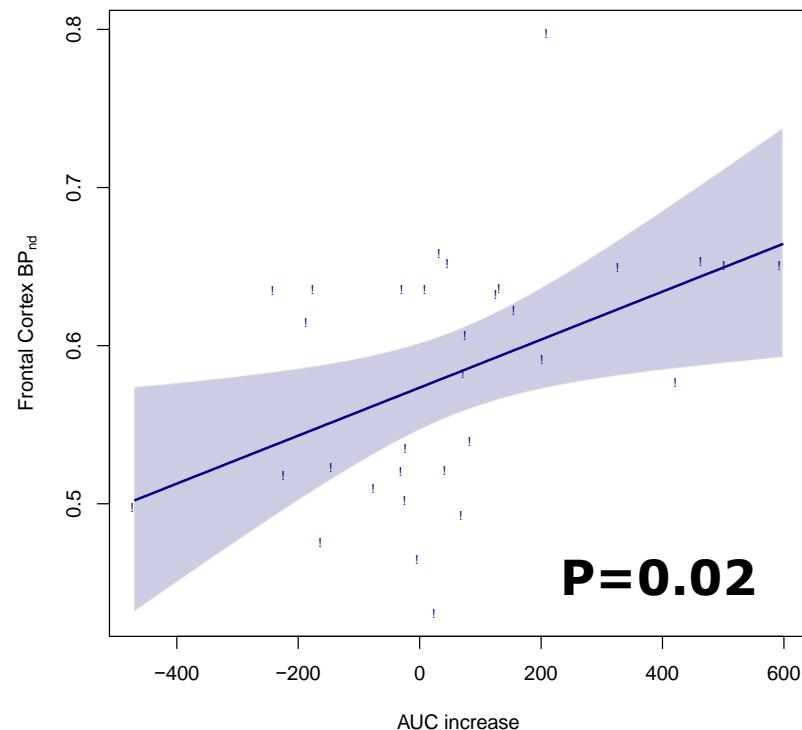
Stress er arvelig – kobling til serotonin



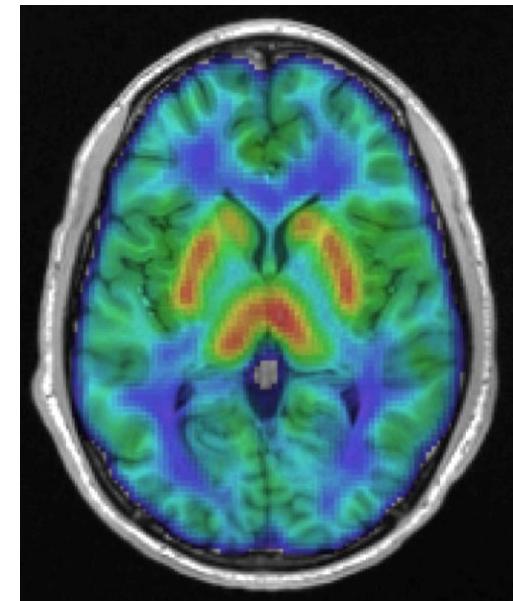
Stress reaktivitet X genotype: Girls homozygous for the s allele produced higher and prolonged levels of cortisol in response to stress than girls with an l allele (N=67). **Gotlib 2008, replicated Way 2009 (N=182)**

Cortisol awakening response (AUCi) and SERT

Positive correlation between prefrontal SERT and CAR



Anterior cingulate: p=0.06



N=32, 7 women
Age: 35.3 (19.7-81.7)
42% L_A/L_A 5-HTTLPR

Ingen interaktion med SERT genotype (5-HTTLPR)

