Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
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The role of steroid hormones and social neuropeptides in Female Adolescent Conduct Disorder

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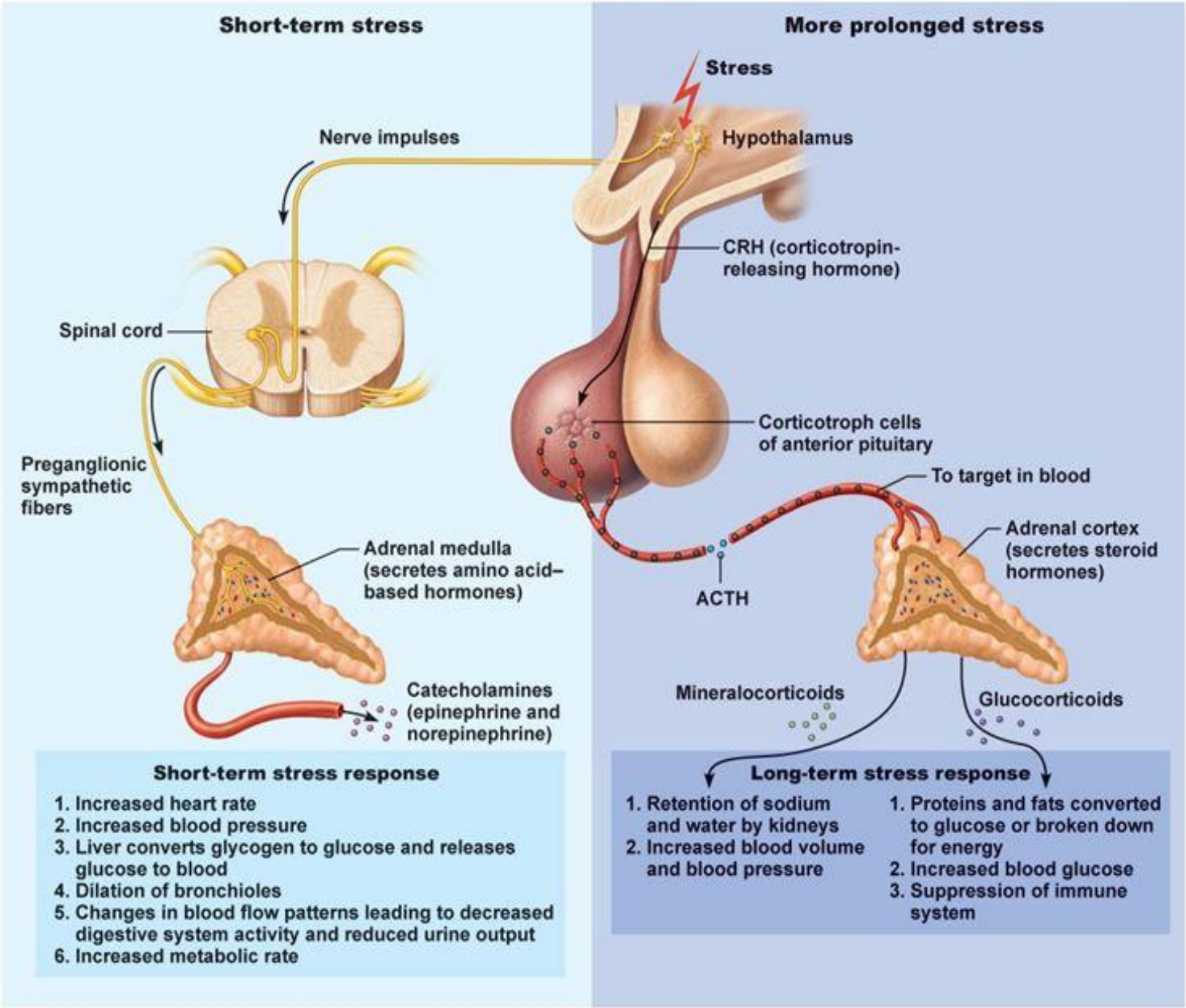
Neurobiology of Conduct disorder

- *Low arousal theory -> stress related systems* ⇩

hormone	function	males with CD	females with CD
Cortisol (CORT)	part of the HPA axis homeostatic regulation / adaptation environment • stress regulation • circadian system • immune system • cardiovascular system	Basal CORT: reduced (Dorn et al. 2009) no differences (Northover et al. 2016) Reactive CORT: reduced (Fairchild et al. 2008, Northover et al. 2016)	Basal CORT: increased (Dorn et al. 2009) reduced (Pajer et al. 2001) no differences (Azar et al. 2004) Reactive CORT: No studies
Alpha Amylase (AA)	enzyme hydrolysis of polysaccharides indicator of adrenergic function (Ditzen et al., 2014)	basal AA: reduced (Angyal et al. 2016, Susman et al. 2010, de Vries-Bouw et al., 2006)	basal AA: no studies


Short-term stress
More prolonged stress
Stress
Nerve impulses
Hypothalamus
CRH (corticotropin-releasing hormone)
Spinal cord
Corticotroph cells of anterior pituitary
Preganglionic sympathetic fibers
To target in blood
Adrenal medulla (secretes amino acid–based hormones)
Adrenal cortex (secretes steroid hormones)
ACTH
Catecholamines (epinephrine and norepinephrine)
Mineralocorticoids
Glucocorticoids
Short-term stress response
1. Increased heart rate
2. Increased blood pressure
3. Liver converts glycogen to glucose and releases glucose to blood
4. Dilation of bronchioles
5. Changes in blood flow patterns leading to decreased digestive system activity and reduced urine output
6. Increased metabolic rate
Long-term stress response
1. Retention of sodium and water by kidneys
2. Increased blood volume and blood pressure
1. Proteins and fats converted to glucose or broken down for energy
2. Increased blood glucose
3. Suppression of immune system

Neurobiology of Conduct disorder

- *Male sex hormones: ↑ aggressive behavior* (Meta-Analysis Book et al. 2001)
- *Female sex hormones: not studied*

hormone	function	males with CD	females with CD
Testo-sterone (TEST)	steroid male sex hormone female / male differences in production and neuronal effects (Morford et al. 2016)	basal TEST: no differences (Constantino et al. 1993, van Goozen et al. 1998, Dorn et al. 2009) reactive TEST: no studies	basal TEST: no differences (Pajer et al. 2006) reactive TEST: no studies
Dehydro-epiandro-sterone (DHEA (-S))	steroid local production in brain (and adrenal gland / gonads) -> metabolites: testosterone & estrogen	basal DHEA (-S): increased (Dimitreiva et al., 2001, Golubchik et al. 2009, van Goozen et al. 1998)) no differences (Dimitreiva et al., 2001)	basal DHEA (-S): reduced (Pajer et al. 2006)

Animal models – aggressive behavior

- *Social neuropeptides* (Haller et al. 2014)

hormone	function	males with CD	females with CD
Oxytocin (OXT)	peptide hormone (Carter 2014) synthesized in PVN hypothalamus • brain and somatic effects • interaction with stress hormone system • muscle contraction (uterus)	basal OXT: reduced (high CD symptoms, high CU traits) (Levy et al. 2015)	basal OXT: no studies
Vaso-pressin (AVP)	peptide hormone (Carter 2014) structurally similar to OXT • water conservation • monogamous behavior • maternal aggression	basal AVP: no studies	basal AVP: no studies

Neurobiology of Conduct disorder

- Contradictory findings

- Few studies on females
- Few studies on reactivity to social stress

- Lack of studies
  - female sex hormones
  - social neuropeptides
  - interaction – despite functional correlation and interaction

Study I basal hormone measures - aims

- Sex specific association of basal cortisol, sex hormones, social neuropeptides, and alpha amylase on CD
- Sex specific interaction between basal cortisol, sex hormones, social neuropeptides, and alpha amylase on CD
- Hypothesis: Sex specific association with CD

FemNAT CD

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„FemNAT-CD“: 17 partners from 7 EU-countries

UK:
Universities of
Birmingham
Southampton
Cardiff

Switzerland:
Basel University
Hospital

Spain:
University Hospitals
in Bilbao &
Barcelona

Netherlands:
Amsterdam
University

Germany:
GU Frankfurt
RWTH Aachen
University
Hospital
Heidelberg
Regensburg
University
4 companies

Hungary:
University
Hospital Szeged

Greece:
University Athens

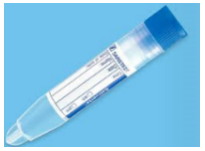
Coordinator: C.M. Freitag, GU Frankfurt am Main

Sample basal hormone measures

	CD female N=111	CONT female N=117	CD male N=71	CONT male N=77	p
Age (mean, SD)	15.3 (2.1)	15.8 (1.9)	14.7 (2.5)	14.9 (2.1)	0.004
Parental education (mean, SD)	6.3 (2.8)	8.5 (3.0)	6.7 (2.6)	8.7 (2.5)	<.001
BMI (mean, SD)	22.6 (4.9)	21.9 (3.9)	20.4 (3.1)	20.7 (3.3)	<.001
Puberty status (N, %)	Early 2 (2) Mid 6 (5) Late 77 (69) Post 26 (23)	Early 2 (2) Mid 6 (5) Late 79 (67) Post 30 (26)	Early 18 (25) Mid 20 (28) Late 31 (44) Post 2 (3)	Early 19 (25) Mid 23 (30) Late 31 (40) Post 4 (5)	<.001
Smoking N (%)	68 (62)	14 (12)	38 (55)	8 (10)	<.001

Exclusion of females with contraceptive use.

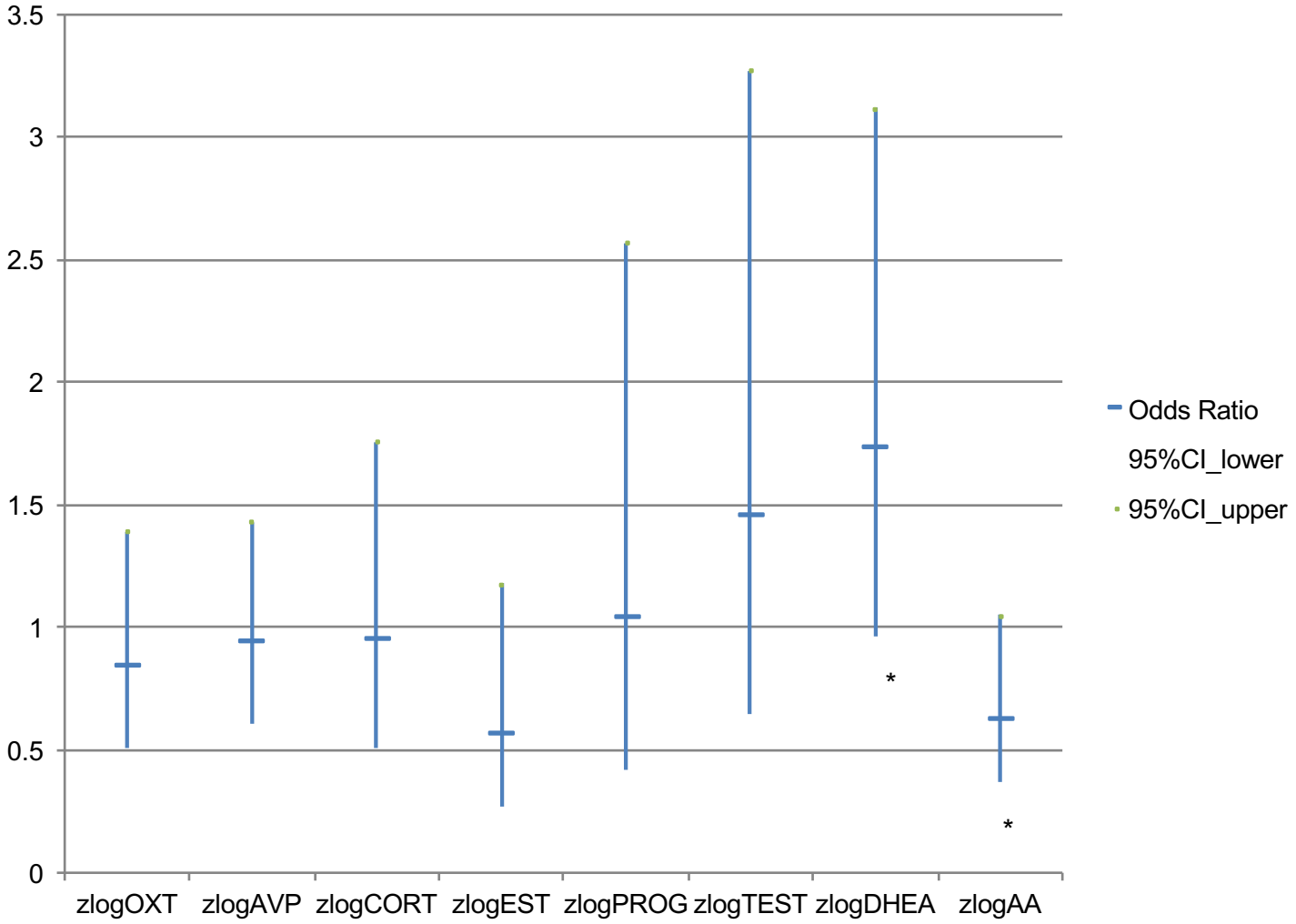
Hormone measures, data analysis



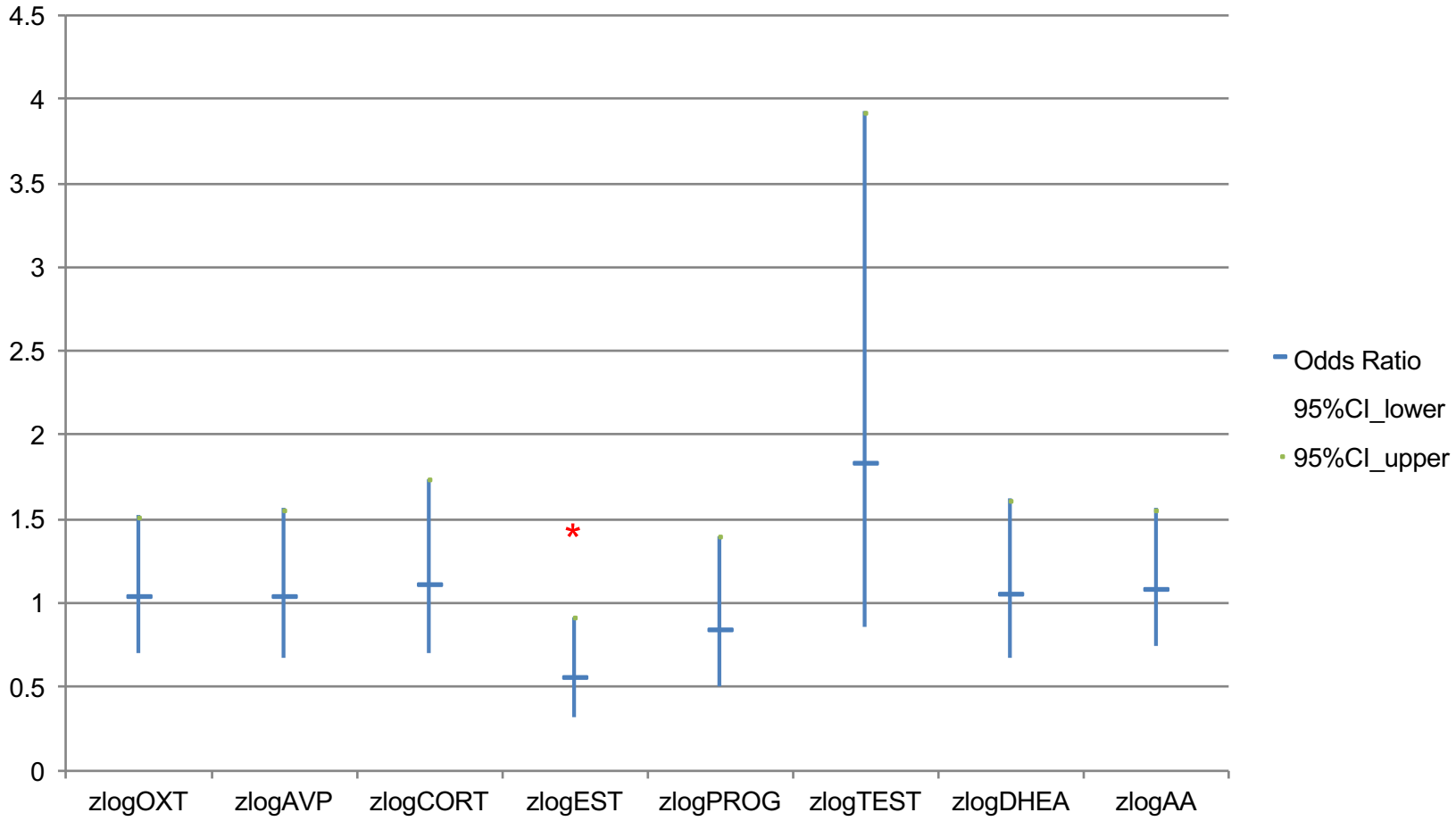
- Salivettes -> OXT, AVP (Riagnosis, Germany)
- Cryotubes –> CORT, TEST, DHEA, EST, PROG, AA (daacro, Germany)
- obtained between 1-6 pm
- no eating, drinking, smoking or stress before sampling
- all hormones were log-transformed and z-standardised for data analysis

- Data analysis 1: – logistic regression, CD as outcome
  - separately males and females
  - matched for puberty status, (time of) menstruation (girls only)
  - all hormones in model
  - adjustment for BMI, smoking, age, time of saliva sampling during day; site (random effect)

Male adolescents: predictors of CD



Female adolescents: predictors of CD



Data analysis 2

- Interaction of hormones
  - instable models for all 2 x 2 fixed effects (64 predictors)
  - Variable reduction by factor analysis

- Logistic regression: CD as outcome
  - factors and interaction of factors as predictors
  - separately males and females
  - matched for puberty status
  - adjustment for BMI, smoking, age, time of saliva sampling during day; site (random effect)

4 factors in males

Rotated Factor Pattern Males

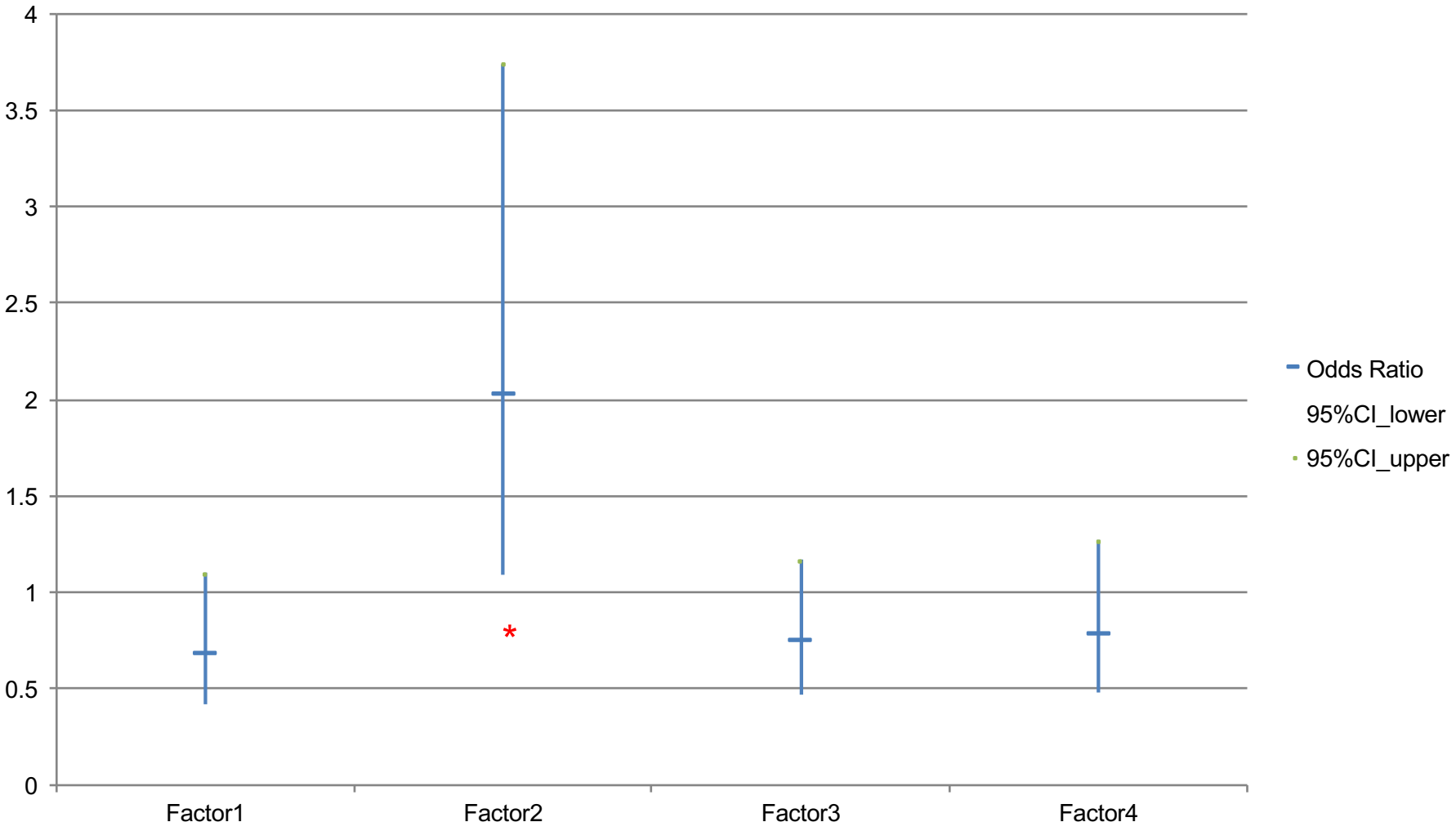
	Factor1	Factor2	Factor3	Factor4
zlogPROG	0.88	0.16	-0.09	-0.10
zlogEST	0.87	0.00	0.21	0.07
zlogDHEA	-0.11	0.88	0.09	0.13
zlogTEST	0.33	0.82	0.12	-0.00
zlogCORT	0.48	0.51	-0.23	-0.35
zlogAA	-0.04	0.03	0.81	0.04
zlogAVP	-0.09	-0.08	-0.66	0.12
zlogOXT	-0.02	0.08	-0.12	0.94

4 factors in females

Rotated Factor Pattern Females

	Factor1	Factor2	Factor3	Factor4
zlogPROG	0.84	-0.15	0.09	-0.12
zlogTEST	0.80	0.21	0.15	0.11
zlogEST	0.79	0.09	-0.13	-0.13
zlogAVP	-0.08	0.80	-0.10	-0.25
zlogDHEA	0.26	0.71	0.16	0.31
zlogAA	-0.11	-0.03	0.88	-0.13
zlogCORT	0.46	0.09	0.60	0.19
zlogOXT	-0.12	-0.03	-0.05	0.89

Male adolescents: predictors of CD



No factor x factor interaction

-> DHEA, TEST, CORT

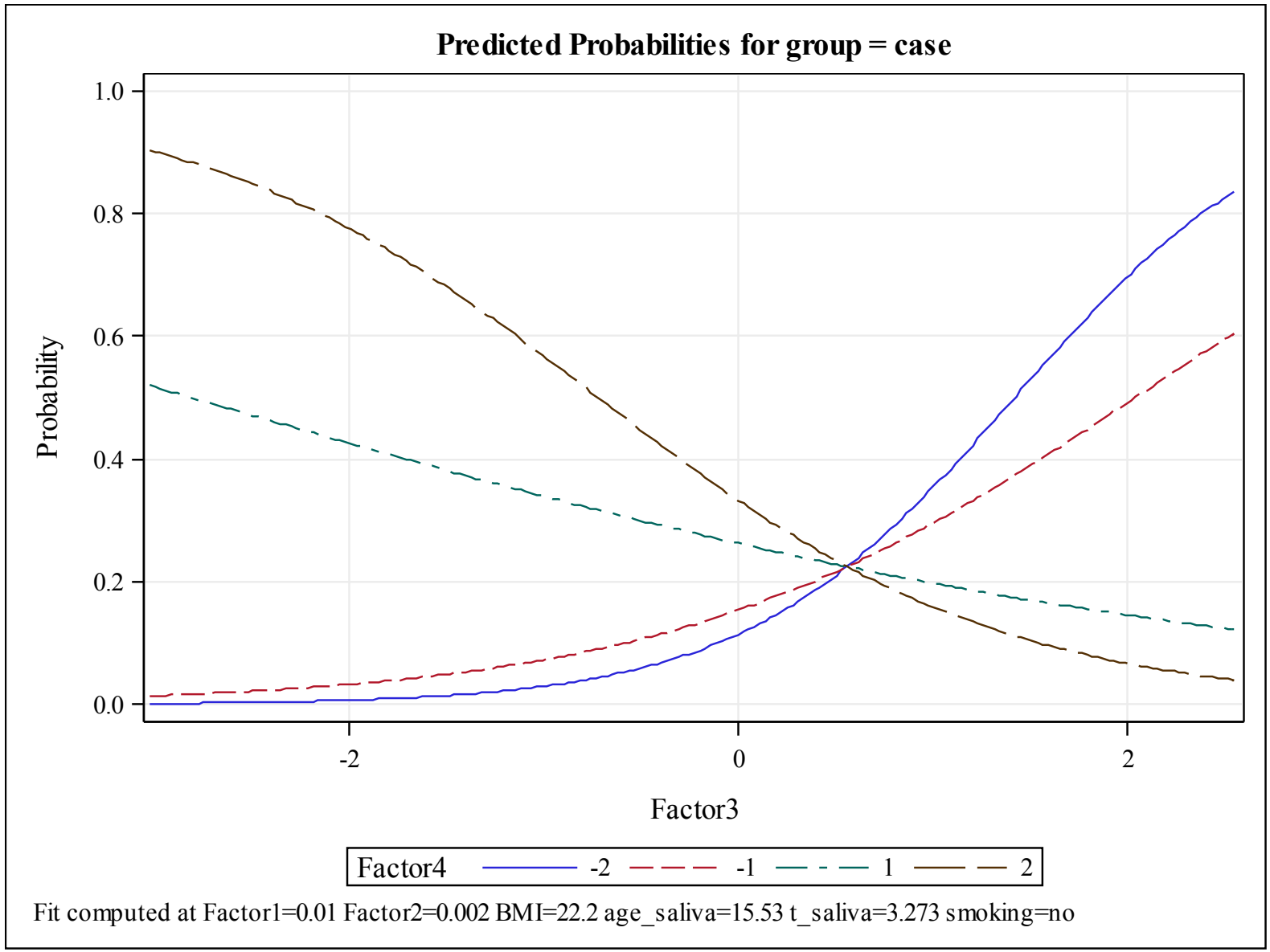
Female adolescents: predictors of CD

Type III Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
Factor1	1	188	2.03	0.1560
Factor2	1	188	0.09	0.7695
Factor3	1	188	1.40	0.2385
Factor4	1	188	2.68	0.1031
Factor1*Factor2	1	188	0.34	0.5610
Factor1*Factor3	1	188	0.02	0.8795
Factor1*Factor4	1	188	1.74	0.1891
Factor2*Factor3	1	188	3.05	0.0824
Factor2*Factor4	1	188	0.30	0.5833
Factor3*Factor4	1	188	6.56	0.0112
smoking	1	188	49.46	<.0001
BMI	1	188	2.71	0.1012
age_saliva	1	188	16.36	<.0001
t_saliva	1	188	5.65	0.0185

Interaction

Factor 3: AA / CORT

Factor 4: OXT



Factor 3: AA / CORT

Factor 4: OXT

Discussion study I

- Difference in basal hormone pattern in males and females
- Female specific CD risk
  - Acute and long-term stress indicators
  - neuropeptides
  - interaction
  - Estradiol?
- Male specific CD risk
  - Male sex hormones

- Pending: exploratory study of risk factors

Study II - aims

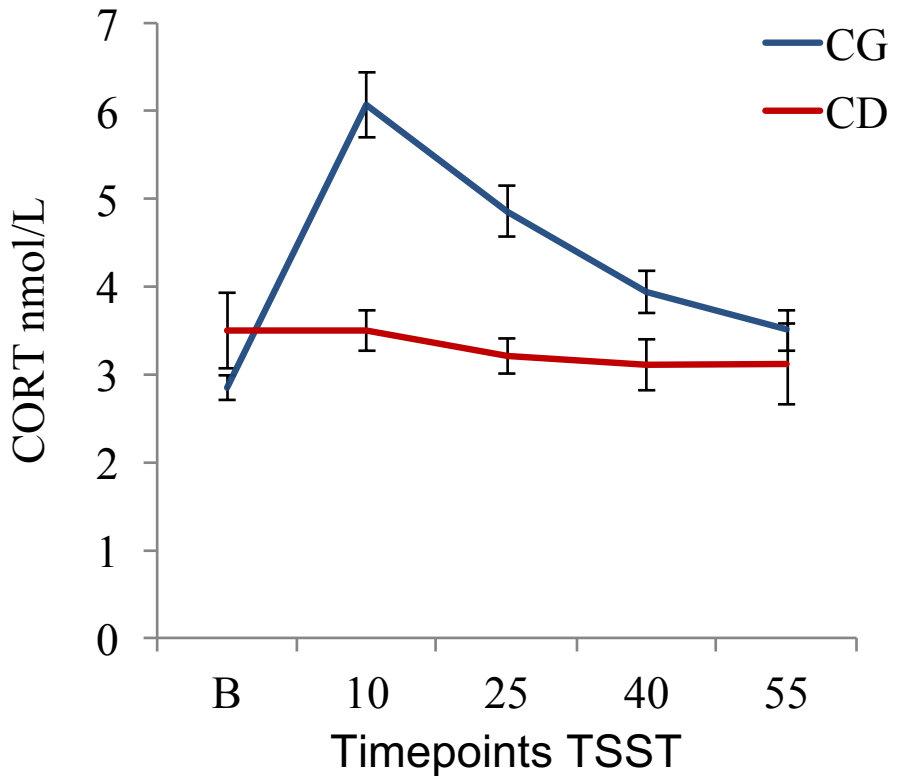
- Trier Social Stress Test (Kirschbaum et al., 1993)

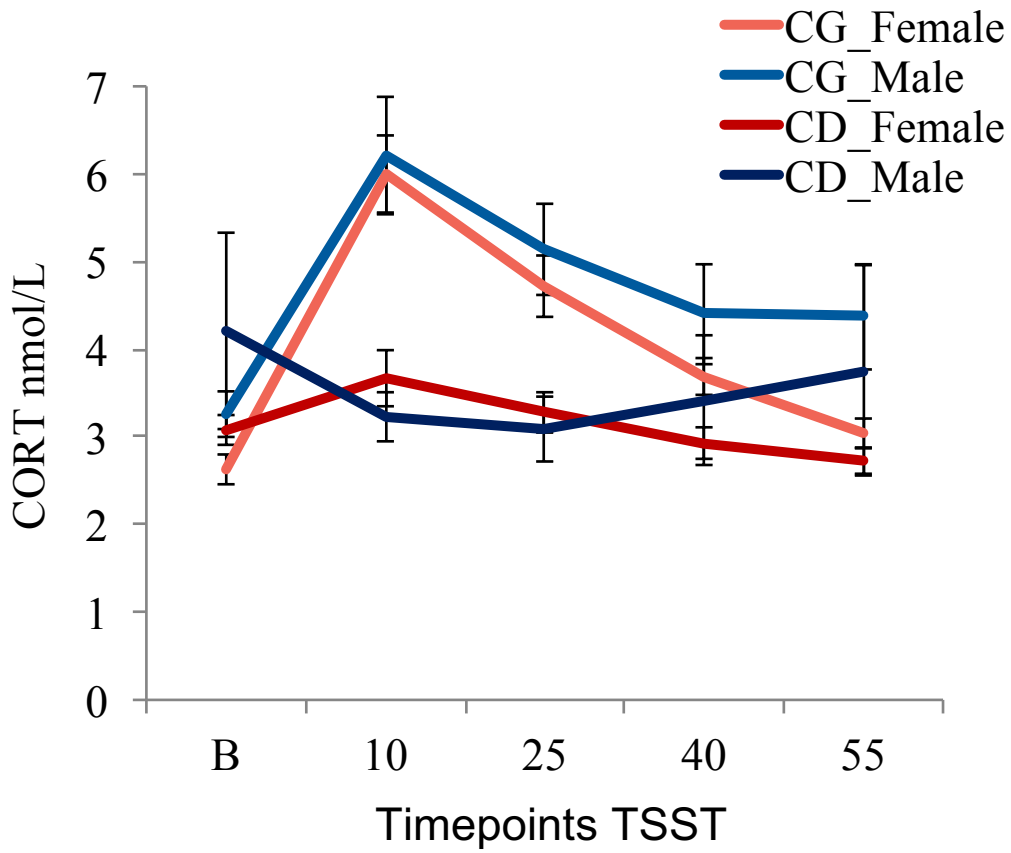
- Comparison of reactive CORT and TEST
- Hypothesis: Attenuated reactive CORT and TEST in CD

Study II sample

	CD	controls	*p*
N = 339	167	172	
♀ (N,%)	105 (63)	112 (65)	
♂	62 (37)	60 (35)	
Age mean (SD)	14.6 (1.9)	14.6 (2.1)	.83
Pubertal Status N (%)	Early 15 (9) Mid 20 (12) Late 101 (63) Post 25 (16)	Early 16 (10) Mid 38 (23) Late 82 (49) Post 33 (20)	.04
BMI mean (SD)	22.32 (4.50)	20.87 (3.63)	<.01
smoking yes/no N (%)	97/68 (59/41)	19/153 (11/89)	<.001
any medication yes/no N (%)	46/111 (29/71)	4/165 (2/98)	<.001

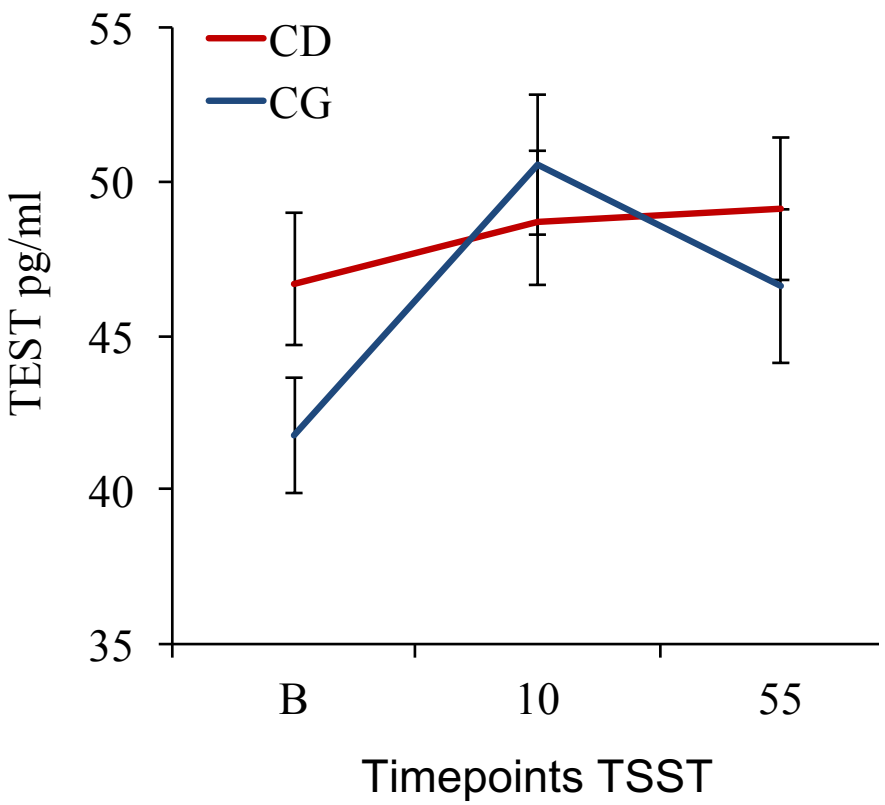
CORT reactivity

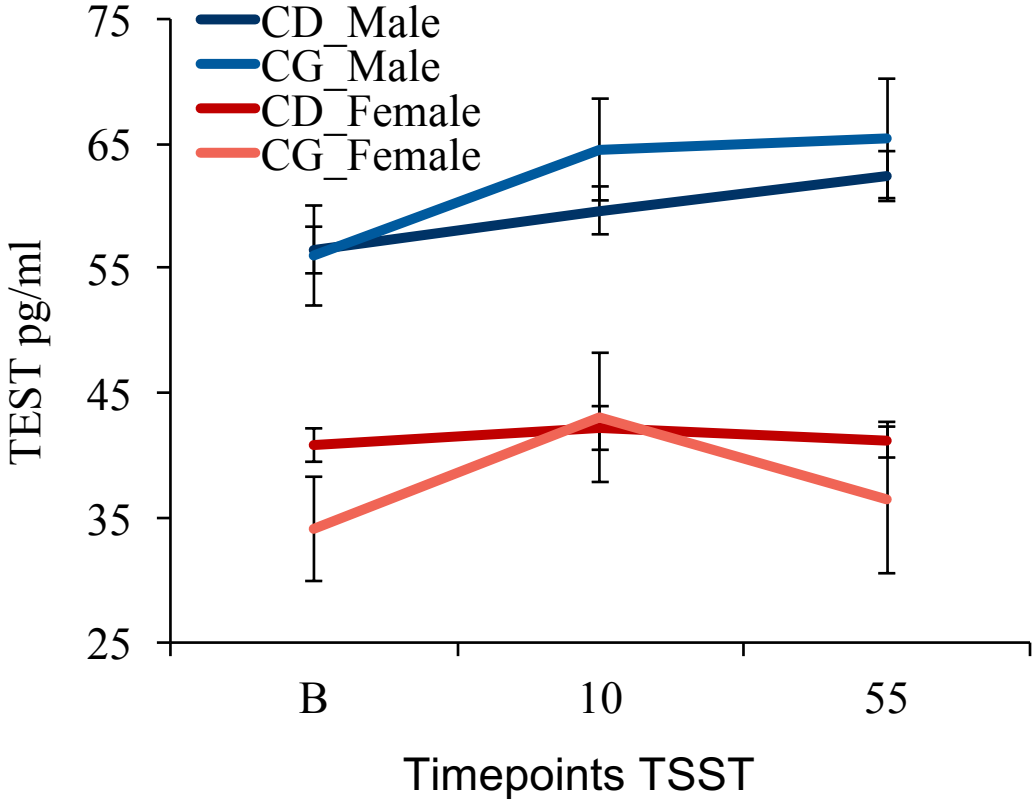




- main effect of group (p<.01, d=.39)
- interaction effect of time*group (p<.001, d=.46)

TEST reactivity





- main effects of time (p<.001, d=.40) and gender (p<.001, d=.87)
- interaction effect of time*group (p<.01, d=.30)

Discussion study II

- CORT / TEST reactivity to social stress
  - Strongly attenuated in CD
  - Gender differences only for TEST

- Pending: exploratory study of risk factors

- Summary:
  - Strong role of stress and sex hormones in adolescent CD
  - May explain increase in CD prevalence in adolescents

Thank you very much

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