Neurodevelopmental Theories of Adolescent Mental Health:
The Cases of Puberty and Early Adversity

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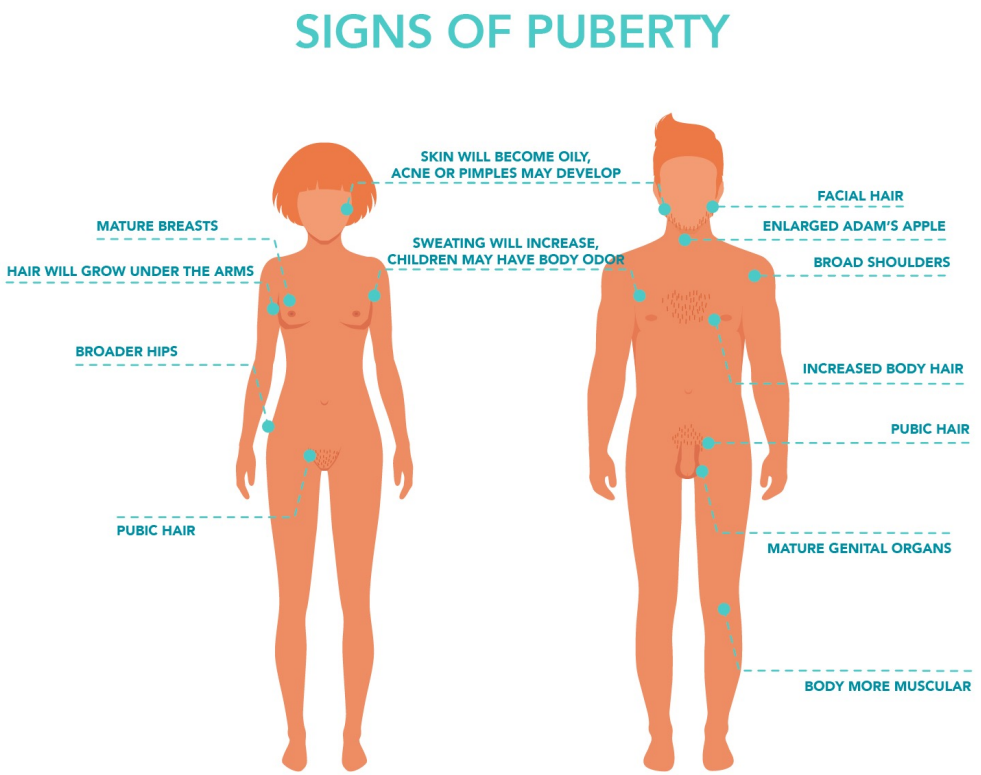
I. Puberty

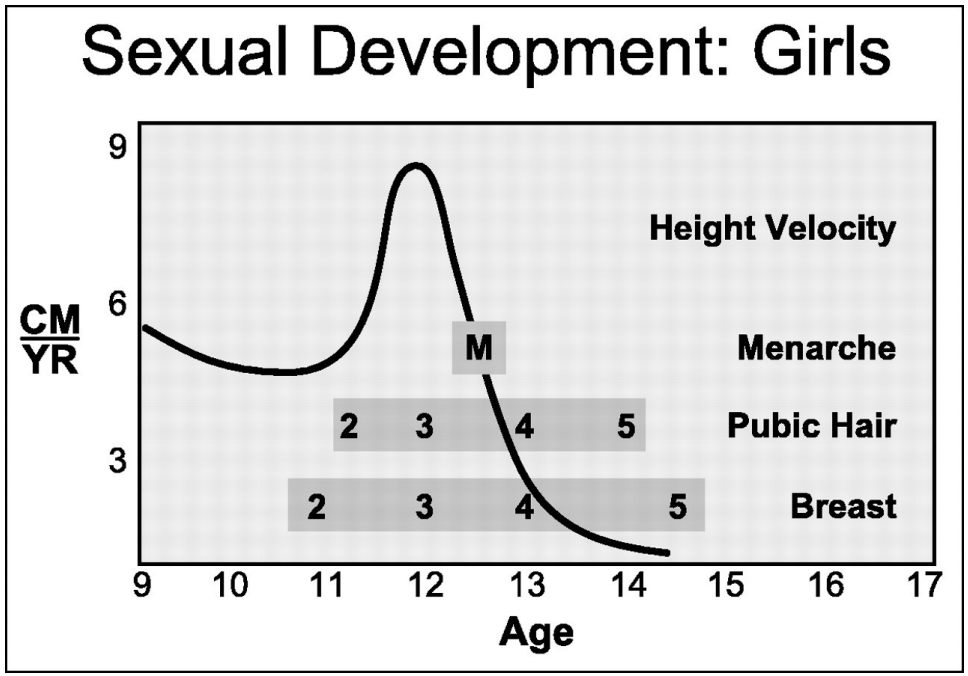
Why study puberty?

- ABCD workshop
- Common definition of adolescence: Adolescence has a biological beginning in puberty – and a social ending with the assumption of adult rights, roles, and responsibilities.

A *multifaceted* "Biological Beginning"

- Multiple phases of puberty:
  - Adrenarche
  - Growth spurt
  - Gonadarche
- Quick reminder: the brain triggers puberty




Sexual Development: Girls
CM
YR
9
6
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Height Velocity
M
Menarche
2 3 4 5
Pubic Hair
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Breast
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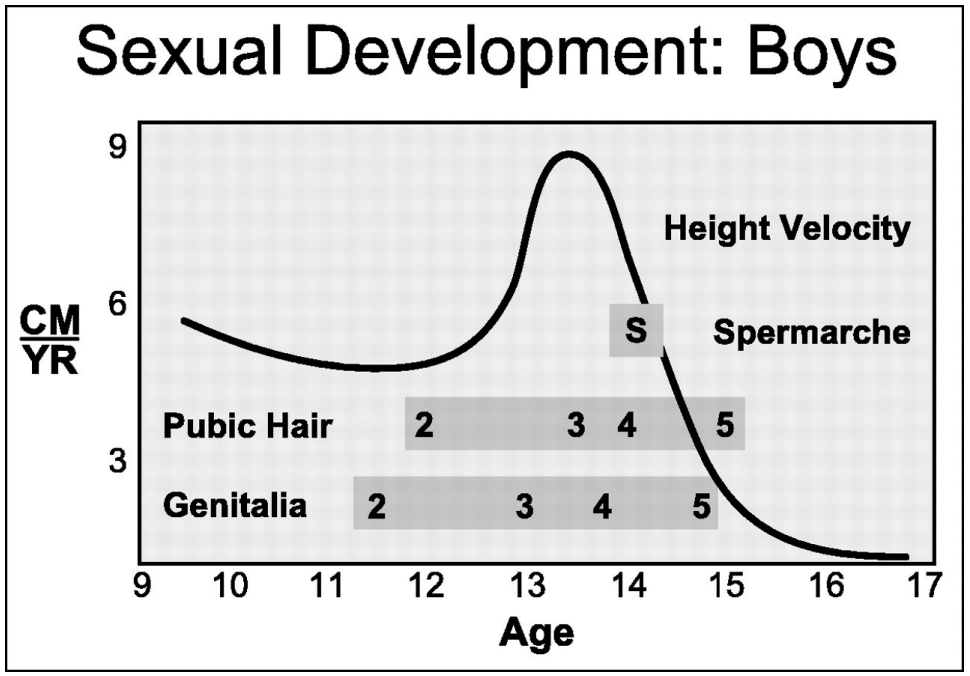
Age


Sexual Development: Boys
CM
YR
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Height Velocity
S
Spermarche
Pubic Hair
2 3 4 5
Genitalia
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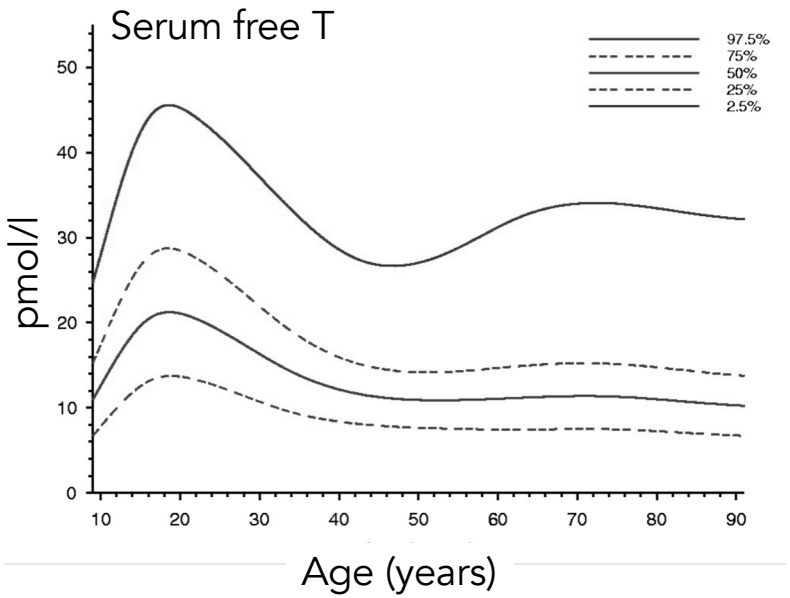
9 10 11 12 13 14 15 16 17
Age

Rosen (2004)

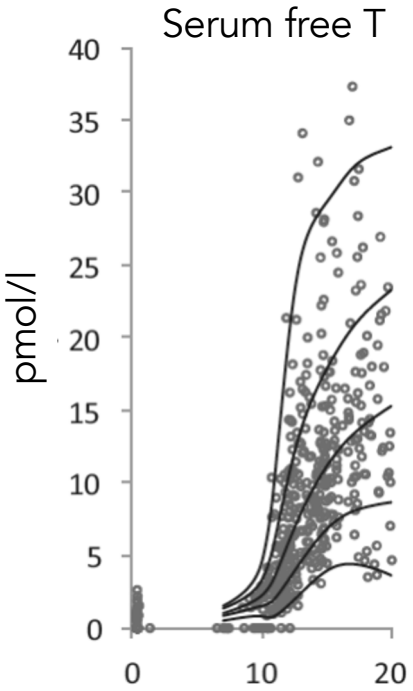
Puberty is a unique measure of maturation

- Different (and in some ways, maybe better) than age during pre/early adolescence
- Pubertal STAGE vs TIMING vs TEMPO
  - STAGE: how 'mature' are you?
  - TIMING: are you early, on-time, or late? (this is relative to same-age, same-sex peers)
  - TEMPO: how fast (or not) are you moving through puberty?
- Note: after secondary sex characteristics finish maturing in mid-adolescence, hormone levels continue to increase until mid-twenties

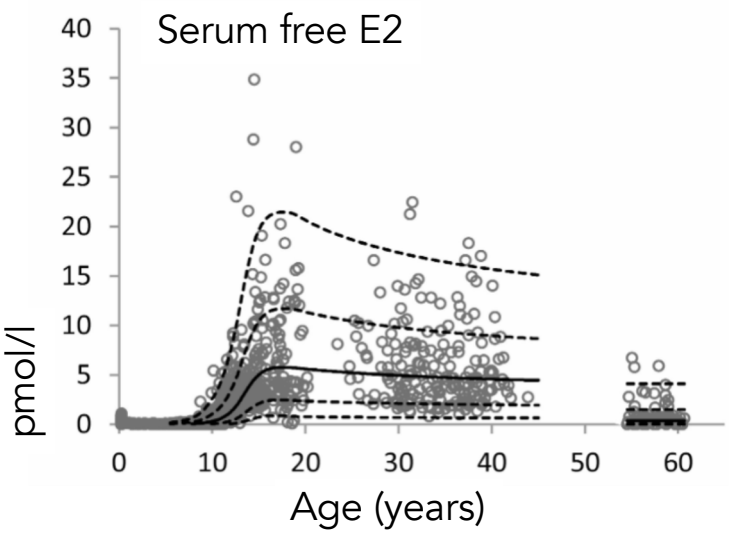
T/E2 peaks around age 20 in girls



Handelsman et al. (2015)

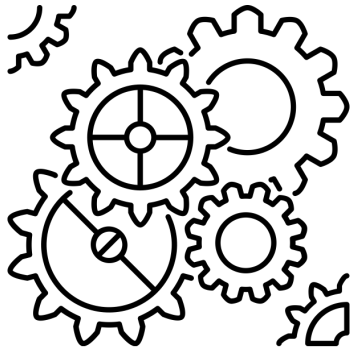


Søeborg et al. (2019)



Frederiksen et al. (2019)

Proposed Mechanisms for Puberty's Impact on Adolescent Mental Health



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from Noun Project

Psychosocial

- Risks of off-time development (maturational deviance)
- Risks of early maturation (developmental readiness, risky social contexts)
- Faster progression through puberty (maturational compression)

Biological

- Hormones
- Brain development
  - Emphasis on reward, positive valence systems
  - Neglect of social processes

Rudolph (2014)

How does puberty impact brain development?: Perspectives from animal models

- Organization-Activation hypothesis about effects of steroid hormones (Sisk & Foster, 2004; Schulz et al., 2009):
  - Organizational effects: Hormones permanently change neural structure (during sensitive periods)
  - Activational effects: Hormones temporarily change activity of neural systems
  - See also Juraska & Willing, 2017

How can we study puberty's impact on *human* brain development & mental health?

- Secondary sexual characteristics
  - Physician/nurse practitioner exams ("Tanner Stages")
  - Self-report (text, line drawings, or photographs)
- Hormones
  - Testosterone, DHEA(-S), Estradiol, Progesterone, FSH, LH
  - How many samples? Saliva? What time of day? Hair?

Specification Curve Analysis of Pubertal Timing & Internalizing

- SCA examines and reports all non-redundant, reasonable, and justifiable measurement/analytic specifications (Simonsohn et al., 2020)
- Reveals the consequences of alternative specifications
- Inferential statistics can be calculated with reference to bootstrapped null distributions

Barendse, Byrne, et al. (under review)
https://psyarxiv.com/p5vfb/

Pubertal Timing (12 predictors)

- Age at menarche
- Subjective timing (PDS item)
- Residual-based:
  - PDS
  - Tanner Stage Line Drawings
  - Adrenal, gonadal, composites
  - Hormone levels (T, E2, DHEA)

Controls

- T1 internalizing
- Early life stress before age 7 (CTQ)

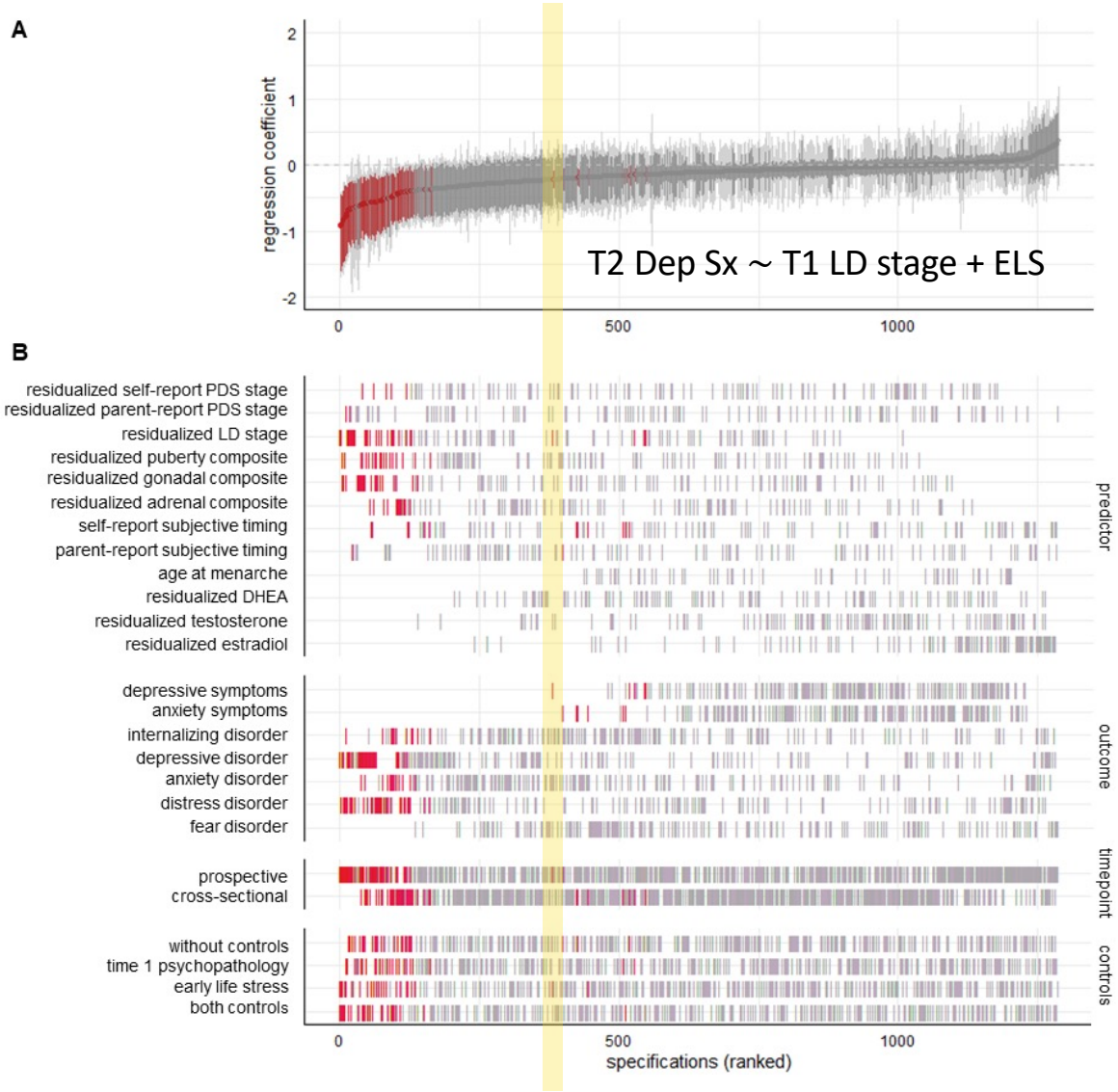
Internalizing (7 outcomes)

- Depression sx: (CES-DC)
- Anxiety sx: SCARED-R
- K-SADS: depressive disorder, anxiety disorder
- HiTOP: distress disorder, fear disorder

Other

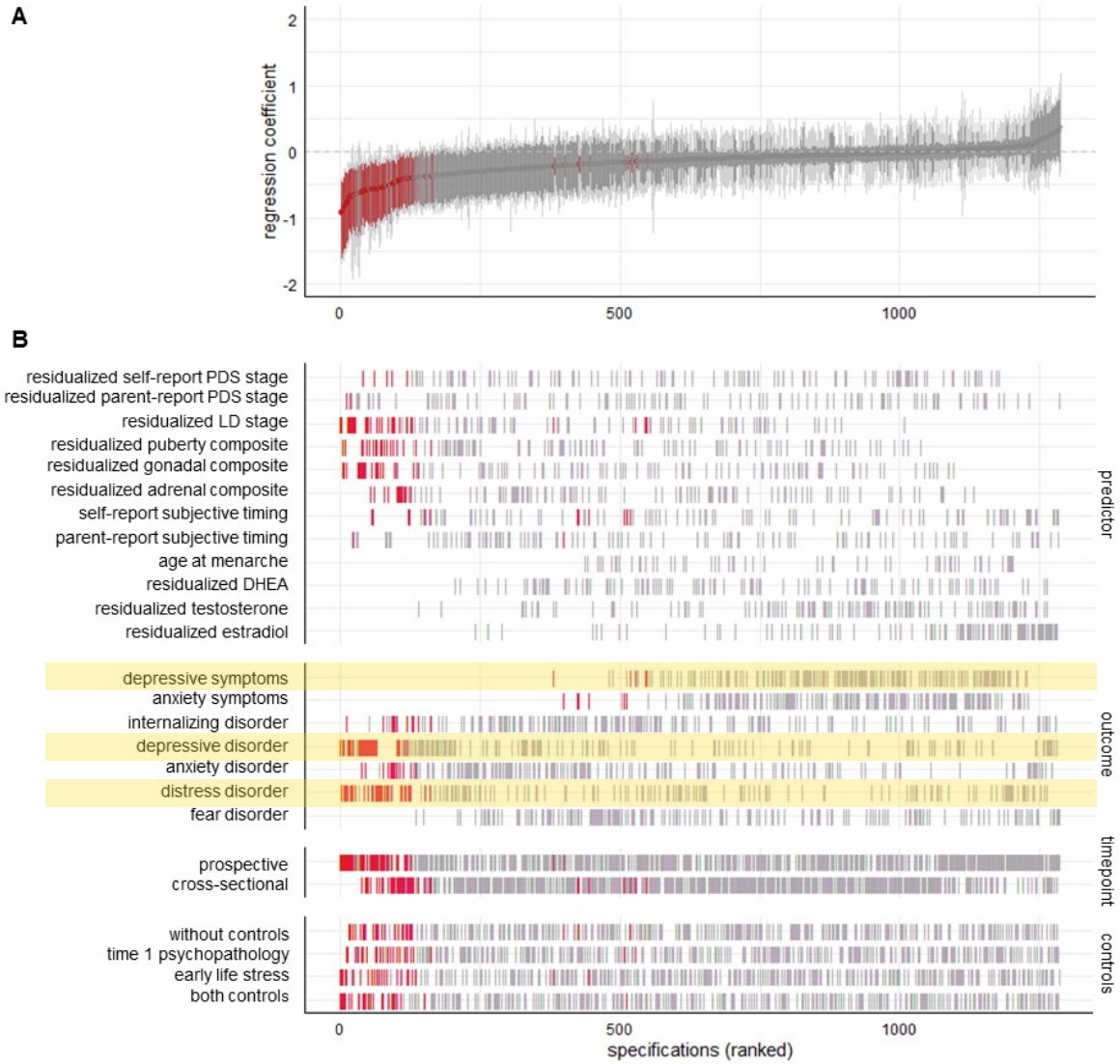
- Prospective vs. Cross-sectional
- Imputation

Total number of model specifications: 1,288



How to read an SCA:

- Each of the 1,288 model specifications is a vertical line
- Red identifies significant models
- Panel A is the regression coefficient of the predictor – rank ordered by size of that coefficient
- Panel B is the corresponding model specification (includes predictors, outcomes, timepoints, & controls)

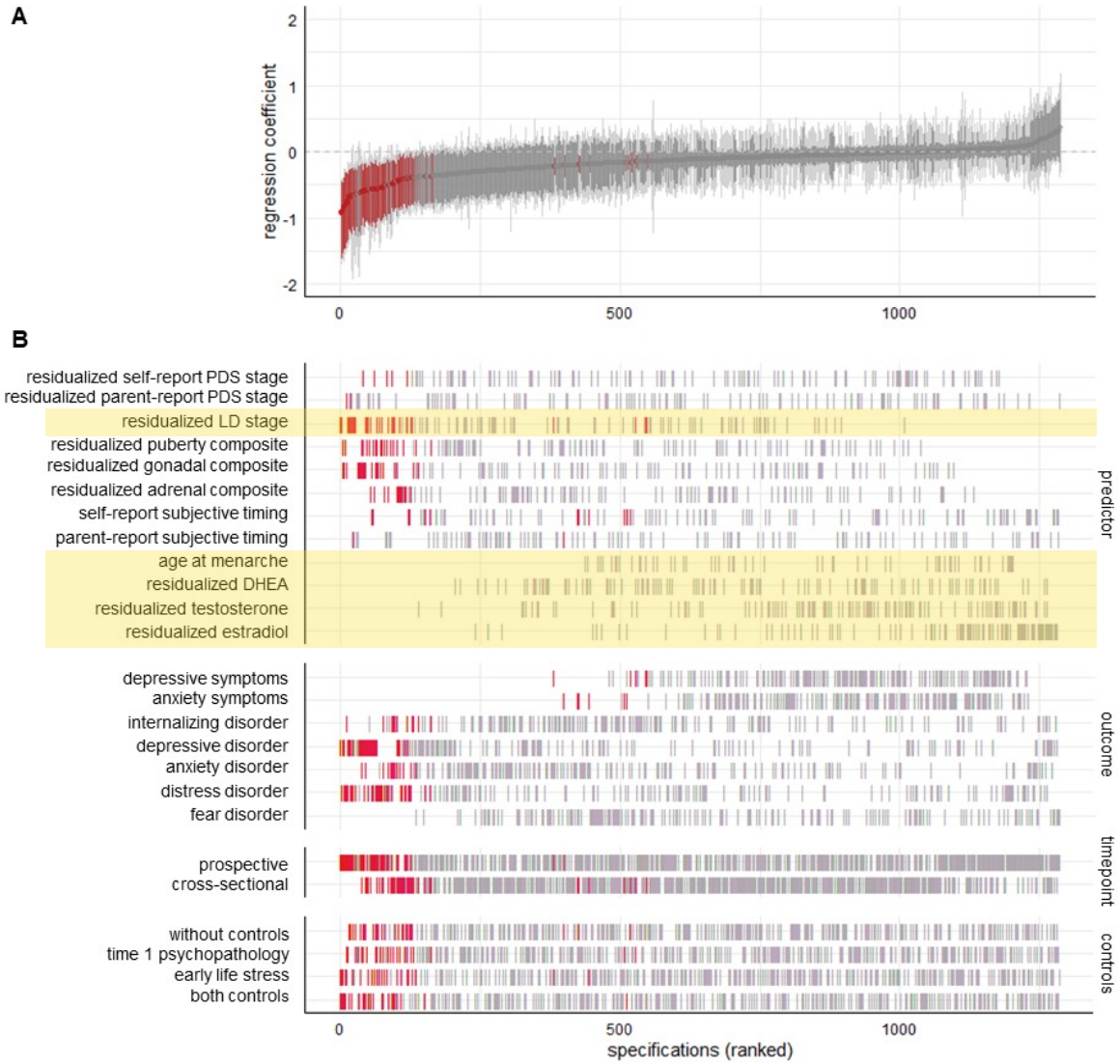


Outcome findings:

- Not many significant results when the outcome is depressive symptoms, and the effect size is smaller
- Many more significant results, with larger effect sizes, when the outcome is depressive disorder (DSM-IV) or distress disorder (HiTOP)

	Median point estimate [confidence interval]		Share of results in negative direction		Share of sign. results in negative direction	
	observed	p	share	p	share	p
Depressive symptoms	-0.04 [-0.06; -0.03]	**<.001**	138/184	**<.001**	5	.580
Anxiety symptoms	-0.04 [-0.06; -0.03]	**<.001**	135/184	**<.001**	6	.280
Internalizing disorder	-0.17 [-0.21; -0.14]	**<.001**	165/184	**<.001**	12	.968
Depressive disorder	-0.29 [-0.34; -0.25]	**<.001**	162/184	**<.001**	43	**<.001**
Anxiety disorder	-0.20 [-0.24; -0.17]	**<.001**	165/184	**<.001**	13	.950
Distress disorder	-0.20 [-0.29; -0.19]	**<.001**	154/184	**<.001**	42	**<.001**
Fear disorder	-0.12 [-0.15; -0.07]	**<.001**	150/184	**<.001**	0	1

Note: Inferential statistics calculated with reference to bootstrapped null distributions



Predictor findings:

- No significant results when age at menarche or any of the hormones served as predictors
- Residualized (age-adjusted) Line Drawings to estimate Tanner Stage was the most effective predictor: most significant results, largest effect sizes

	Prospective						Cross-sectional						Combined					
	Median point estimate [CI]		Share of results in negative direction		Share of sign. results in negative direction		Median point estimate [CI]		Share of results in negative direction		Share of sign. results in negative direction		Median point estimate [CI]		Share of results in negative direction		Share of sign. results in negative direction	
	observed	p	share	p	share	p	observed	p	share	p	share	p	observed	p	share	p	share	p
Residualized self-report PDS stage	-0.16 [-0.21; -0.08]	**<.001**	48/66	**<.001**	6	.232	-0.09 [-0.14; -0.06]	**.002**	52/66	**<.001**	0	1	-0.11 [-0.15; -0.07]	**<.001**	100/112	**<.001**	6	.914
Residualized parent-report PDS stage	-0.15 [-0.23; -0.09]	**.002**	48/66	**<.001**	2	.980	-0.12 [-0.15; -0.04]	**<.001**	50/66	**<.001**	0	1	-0.13 [-0.16; -0.08]	**<.001**	98/112	**<.001**	2	1
Residualized LD Tanner stage	-0.28 [-0.36; -0.20]	**<.001**	56/66	**<.001**	20	**<.001**	-0.29 [-0.34; -0.19]	**<.001**	56/66	**<.001**	18	**<.001**	-0.29 [-0.32; -0.21]	**<.001**	112/112	**<.001**	38	**<.001**
Residualized puberty composite	-0.23 [-0.30; -0.15]	**<.001**	56/66	**<.001**	17	**<.001**	-0.19 [-0.26; -0.13]	**<.001**	56/66	**<.001**	5	.448	-0.22 [-0.26; -0.16]	**<.001**	112/112	**<.001**	22	**<.001**
Residualized gonadal composite	-0.21 [-0.29; -0.18]	**<.001**	56/66	**<.001**	17	**<.001**	-0.17 [-0.21; -0.10]	**<.001**	53/66	**<.001**	7	.108	-0.18 [-0.23; -0.14]	**<.001**	109/112	**<.001**	24	**<.001**
Residualized adrenal composite	-0.18 [-0.23; -0.10]	**<.001**	50/66	**<.001**	9	**.014**	-0.19 [-0.22; -0.12]	**<.001**	56/66	**<.001**	6	.236	-0.18 [-0.21; -0.13]	**<.001**	106/112	**<.001**	15	**.008**
Self-report subjective timing	0.01 [-0.08; 0.03]	.384	30/66	.650	2	.994	-0.17 [-0.22; -0.13]	**<.001**	56/66	**<.001**	10	**.014**	-0.11 [-0.15; -0.07]	**<.001**	82/112	**<.001**	12	.162
Parent-report subjective timing	-0.17 [-0.21; -0.10]	**<.001**	45/66	**<.001**	2	.982	-0.18 [-0.20; -0.08]	**<.001**	51/66	**<.001**	0	1	-0.17 [-0.18; -0.10]	**<.001**	96/112	**<.001**	2	1
Age at menarche	NA		NA		NA		NA		NA		NA		-0.07 [-0.09; 0]	**.028**	38/56	**.012**	0	1
Residualized DHEA	-0.15 [-0.17; -.06]	**<.001**	48/66	**<.001**	0	1	-0.06 [-0.11; 0]	**.002**	44/66	**<.001**	0	1	-0.11 [-0.12; -0.04]	**<.001**	92/112	**<.001**	0	1
Residualized testosterone	-0.05 [-0.08; 0.03]	.060	36/66	.056	0	1	-0.03 [-0.08; 0.01]	.170	49/66	**<.001**	0	1	-0.04 [-0.07; 0.01]	**.030**	85/112	**<.001**	0	1
Residualized estradiol	0.08 [0.04; 0.14]	**.002**	53/66	**<.001**	0	1	-0.03 [-0.08; 0.02]	.396	36/66	**.032**	0	1	0.03 [0; 0.07]	.084	73/112	**.002**	0	1
All predictors combined	-0.11 [-0.13;-0.09]	**<.001**	510/616	**<.001**	75	**<.001**	-0.11 [-0.13;-0.10]	**<.001**	597/616	**<.001**	46	.29	-0.11 [-0.13;-0.10]	**<.001**	1069/1288	**<.001**	121	**.002**

Note: DHEA = Dehydroepiandrosterone; CI = confidence interval; LD = Tanner Stage Line Drawings; PDS = Pubertal Development Scale.

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Note: DHEA = Dehydroepiandrosterone; CI = confidence interval; LD = Tanner Stage Line Drawings; PDS = Pubertal Development Scale.

Insights from the SCA

- Strongest associations between pubertal timing & internalizing if:
  - Pubertal timing was measured by **Tanner Stage Line Drawings**
  - Internalizing outcome was **case-level disorders (DSM-IV depression or HiTOP distress,** coded from K-SADS diagnostic interviews)
- Timing from **hormone** levels was **not** associated with internalizing
  - Suggests **psychosocial** mechansisms may be more meaningful determinants than biological ones in early adolescent girls
- **Prospective** associations more often significant than cross-sectional
  - Suggests initial steps in pubertal process may be particularly salient
  - Controlling for W1 internalizing did not weaken results, indicates likely direction of effect is from pubertal timing → internalizing

How does ABCD do it?

- Parent and self report on the Pubertal Development Scale (Petersen et al., 1988)
- 1 saliva sample (DHEA, T; and E2 in girls)

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PERSPECTIVE article

Front. Endocrinol., 05 May 2021 | https://doi.org/10.3389/fendo.2021.608575

Check for updates

A Researcher's Guide to the Measurement and Modeling of Puberty in the ABCD Study® at Baseline

Theresa W. Cheng[1*], Lucía Magis-Weinberg[2], Victoria Guazzelli Williamson[1], Cecile D. Ladouceur[3], Sarah L. Whittle[4], Megan M. Herting[5], Kristina A. Uban[6], Michelle L. Byrne[1,7], Marjolein E. A. Barendse[1], Elizabeth A. Shirtcliff[8] and Jennifer H. Pfeifer[1]

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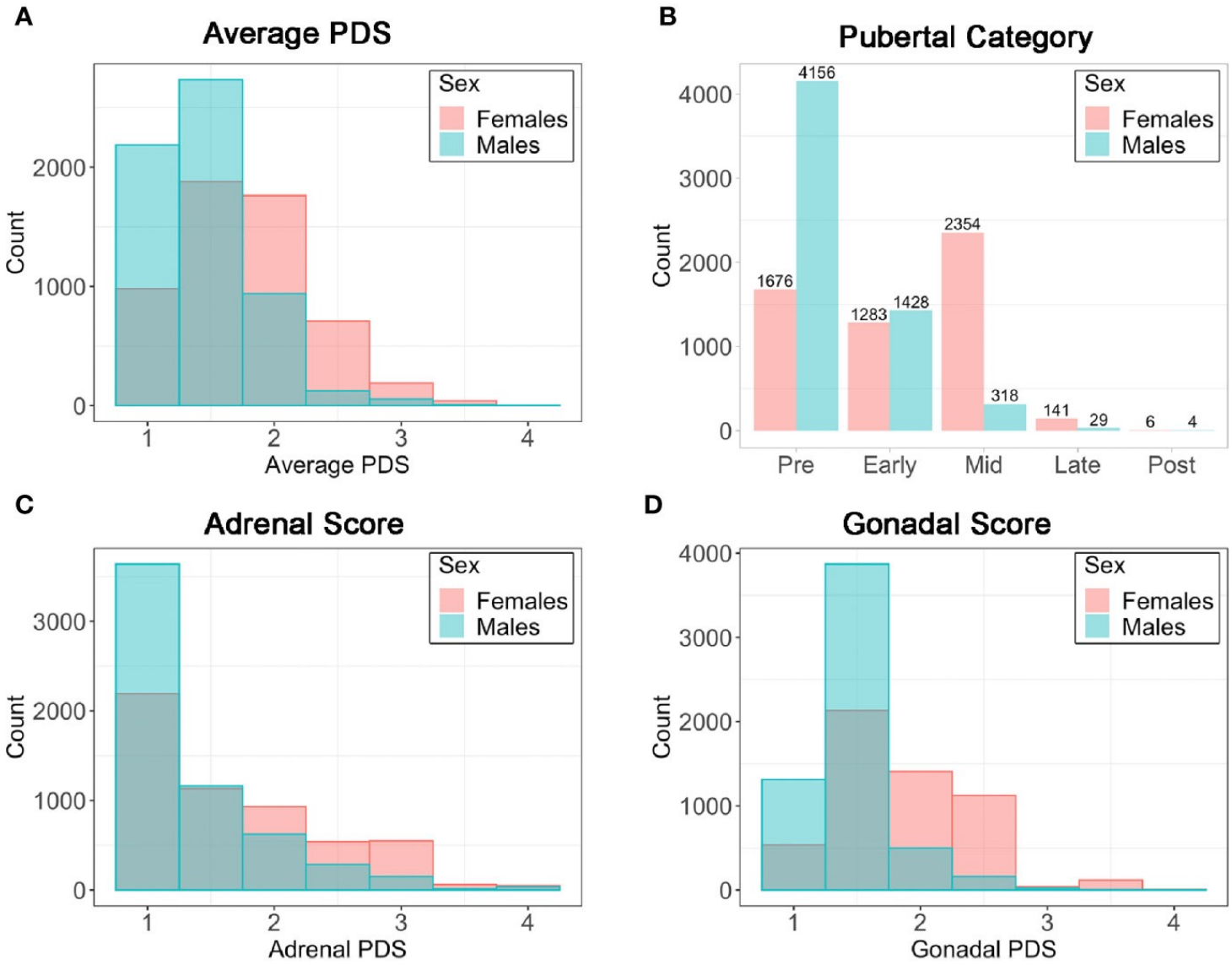
ORIGINAL RESEARCH article

Front. Endocrinol., 18 February 2021 | https://doi.org/10.3389/fendo.2020.549928

Correspondence Between Perceived Pubertal Development and Hormone Levels in 9-10 Year-Olds From the Adolescent Brain Cognitive Development Study

 Megan M. Herting[1,2*†],  Kristina A. Uban[3,4*†], Marybel Robledo Gonzalez[5,6],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Average PDS
Sex
Females
Males
Count
Average PDS
B
Pubertal Category
4156
1676
1283
1428
2354
318
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Adrenal Score
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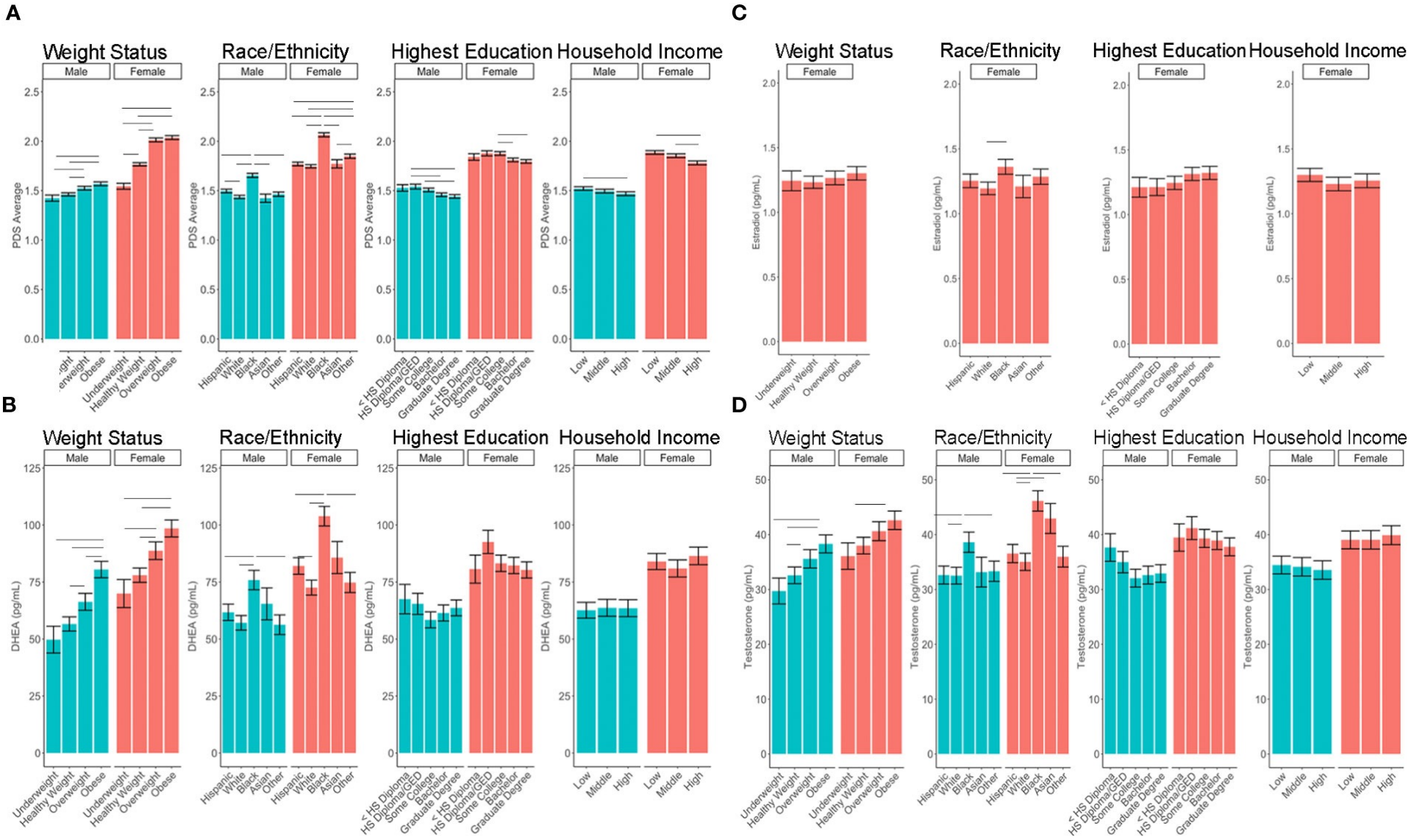
Gonadal Score
Gonadal PDS


A
Weight Status
Race/Ethnicity
Highest Education
Household Income
Male
Female
PDS Average
Underweight
Healthy Weight
Overweight
Obese
Hispanic
White
Black
Asian
Other
< HS Diploma
HS Diploma/GED
Some College
Bachelor
Graduate Degree
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Middle
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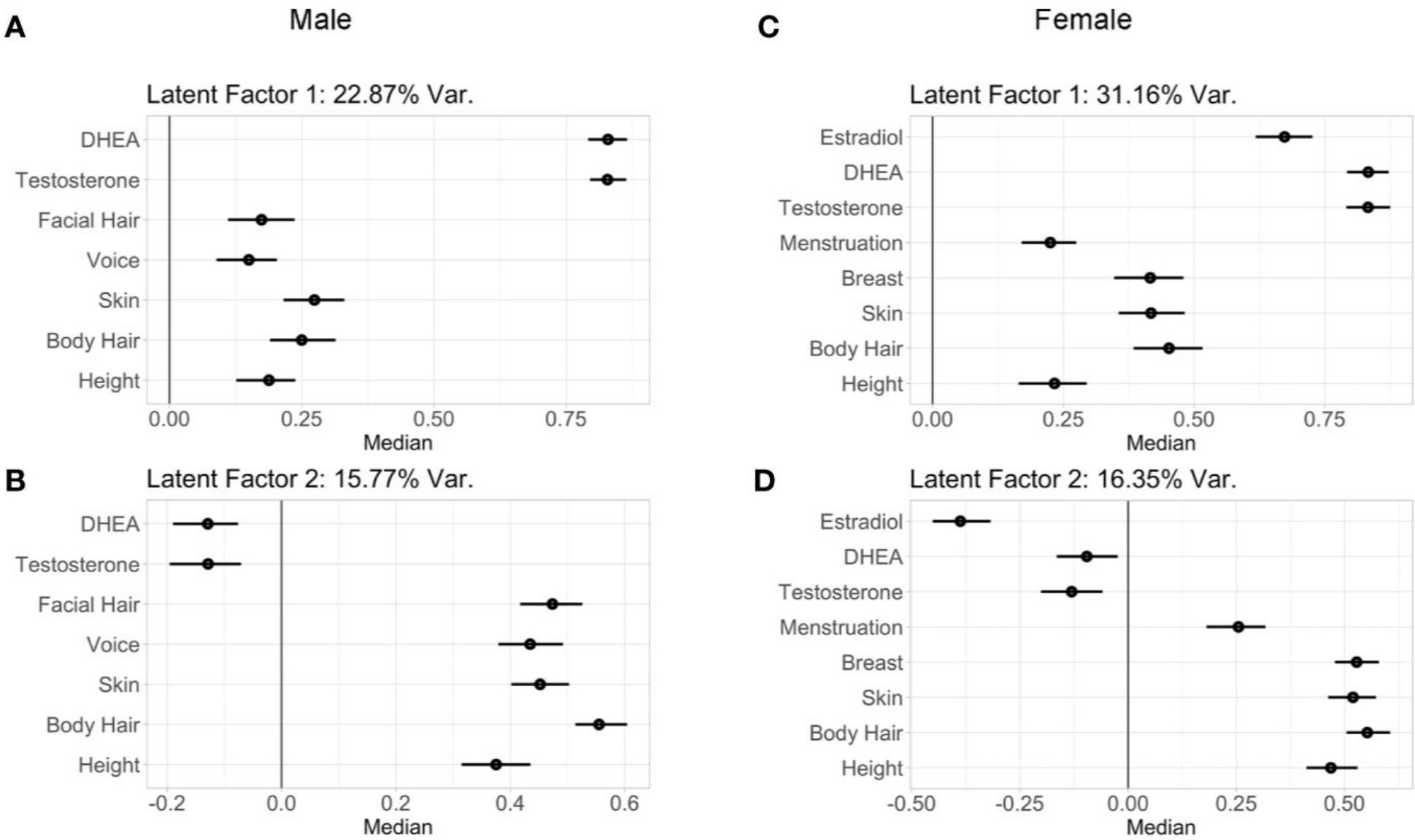
DHEA (pg/mL)
C
Estradiol (pg/mL)
D
Testosterone (pg/mL)


A
Male
Latent Factor 1: 22.87% Var.
DHEA
Testosterone
Facial Hair
Voice
Skin
Body Hair
Height
0.00
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0.50
0.75
Median
B
Latent Factor 2: 15.77% Var.
DHEA
Testosterone
Facial Hair
Voice
Skin
Body Hair
Height
-0.2
0.0
0.2
0.4
0.6
Median
C
Female
Latent Factor 1: 31.16% Var.
Estradiol
DHEA
Testosterone
Menstruation
Breast
Skin
Body Hair
Height
0.00
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Median
D
Latent Factor 2: 16.35% Var.
Estradiol
DHEA
Testosterone
Menstruation
Breast
Skin
Body Hair
Height
-0.50
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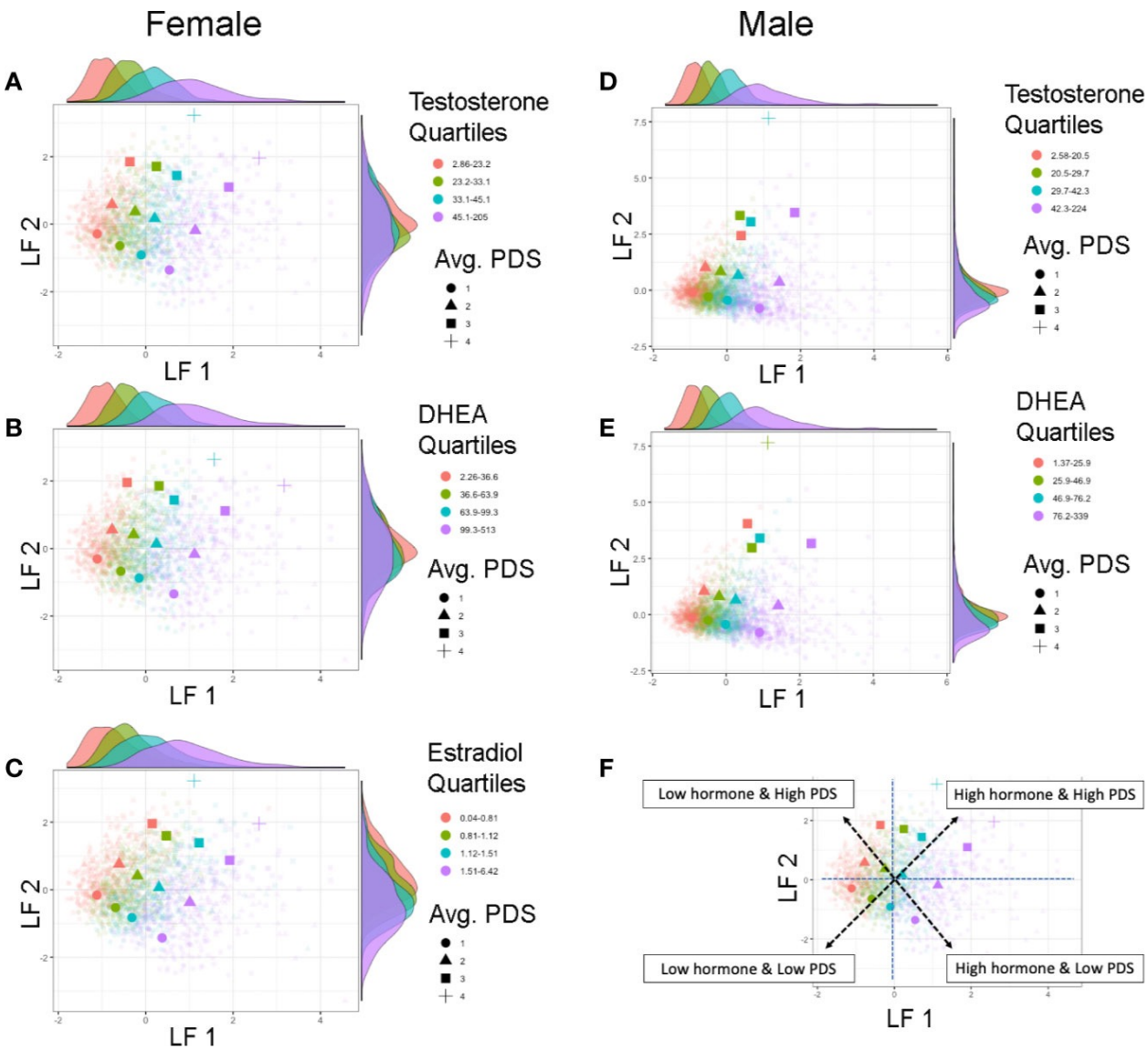
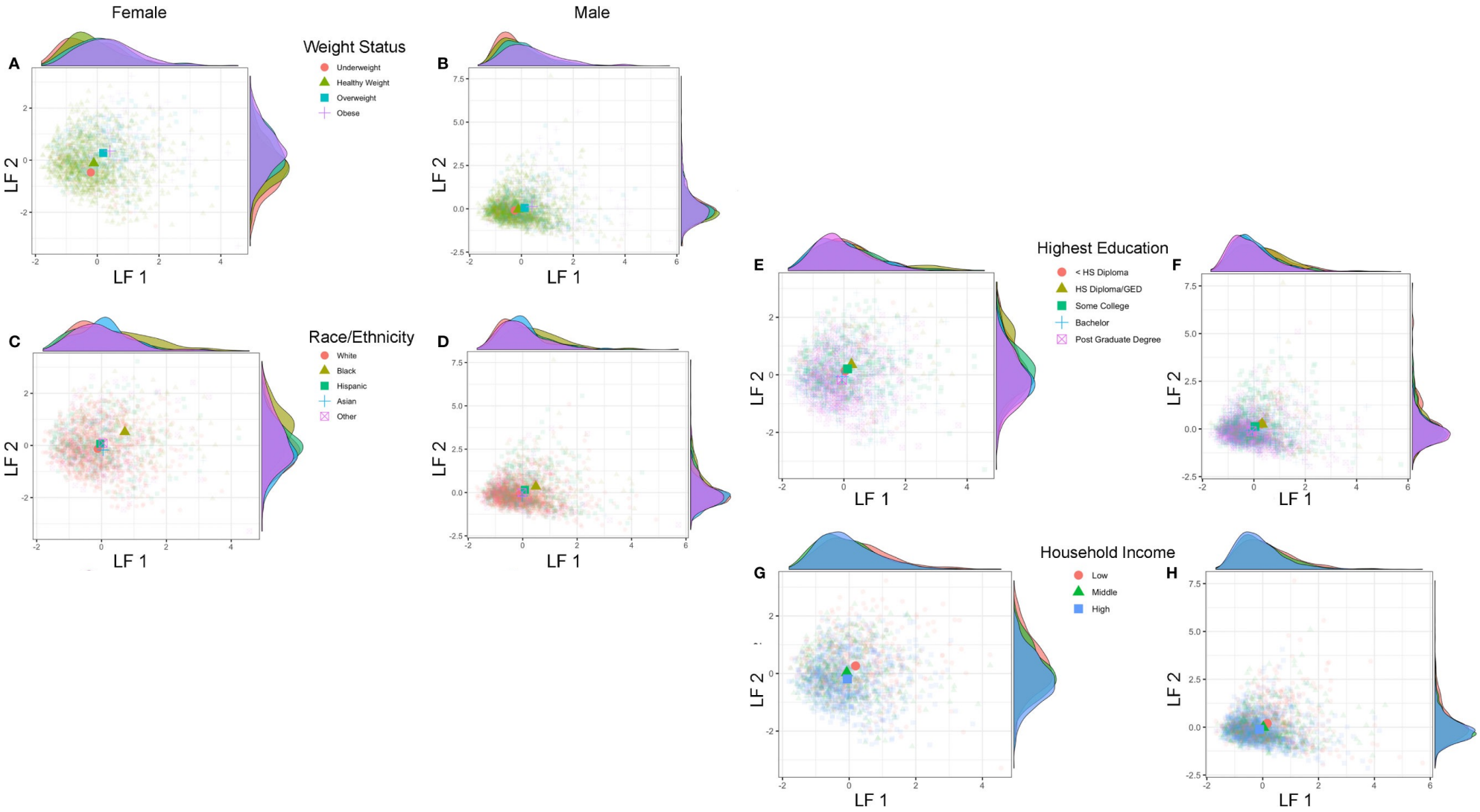

Female
Male
A
B
C
D
E
F
LF 1
LF 2
Testosterone Quartiles
2.86-23.2
23.2-33.1
33.1-45.1
45.1-205
DHEA Quartiles
2.26-36.6
36.6-63.9
63.9-99.3
99.3-513
Estradiol Quartiles
0.04-0.81
0.81-1.12
1.12-1.51
1.51-6.42
Testosterone Quartiles
2.58-20.5
20.5-29.7
29.7-42.3
42.3-224
DHEA Quartiles
1.37-25.9
25.9-46.9
46.9-76.2
76.2-339
Avg. PDS
1
2
3
4
Low hormone & High PDS
High hormone & High PDS
Low hormone & Low PDS
High hormone & Low PDS


Female
Male
A
B
C
D
E
F
G
H
Weight Status
Underweight
Healthy Weight
Overweight
Obese
Race/Ethnicity
White
Black
Hispanic
Asian
Other
Highest Education
< HS Diploma
HS Diploma/GED
Some College
Bachelor
Post Graduate Degree
Household Income
Low
Middle
High
LF 1
LF 2

Handy reviews to bookmark on puberty & neurodevelopment

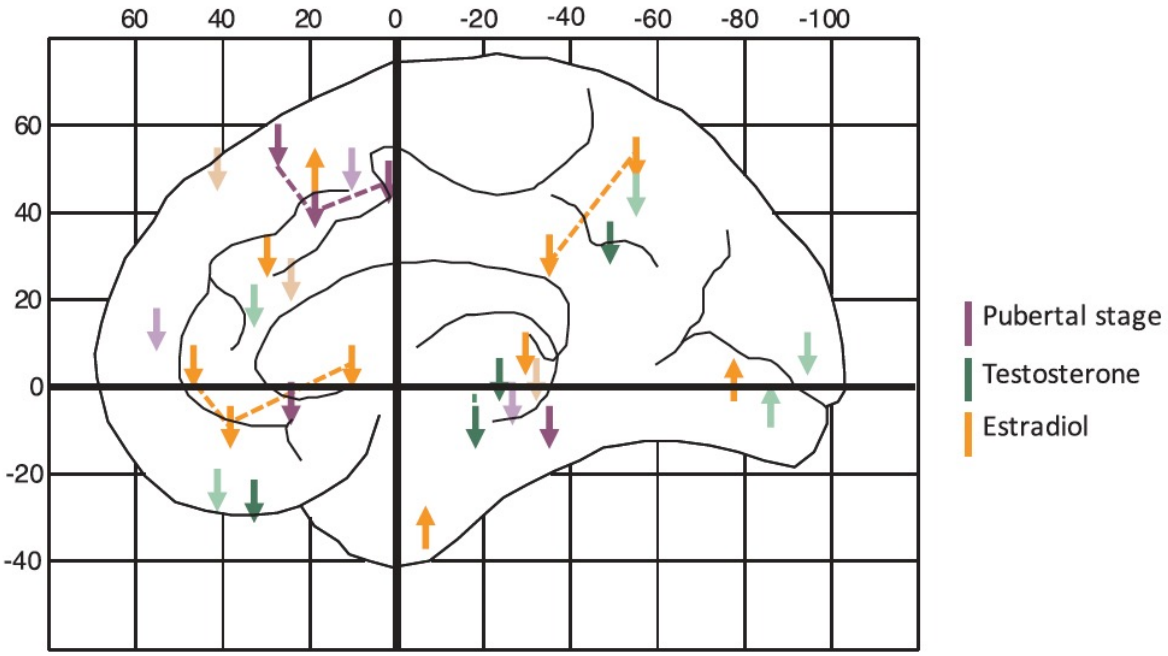
- Vijayakumar, Op de Macks, Shirtcliff, & Pfeifer (2018) – all neuroimaging modalities
- Byrne et al. (2017) – adrenarche
- Herting & Sowell (2017) – structure
- Goddings et al. (2019) – structure
- Dai & Sherf (2019) – fMRI/EEG
- Barendse & Pfeifer (forthcoming Handbook of Dev Cog Neuro)

Puberty and global cortical GM (Vijayakumar et al., 2018)

	Without Age		With Age		Age	Sample size
	Female	Male	Female	Male		
Pubertal stage						
Peper et al., 2009b					9	214
Koolschijn et al., 2014					8-25	215
Bramen et al., 2011					10-14	80
Pfefferbaum et al., 2015					12-22	674
Testosterone						
Peper et al., 2009c					10-15	78
Koolschijn et al., 2014					8-25	215
Bramen et al., 2011					10-14	80
Paus et al., 2010					12-18	419
Estradiol						
Peper et al., 2009c					10-15	78
Koolschijn et al., 2014					8-25	215

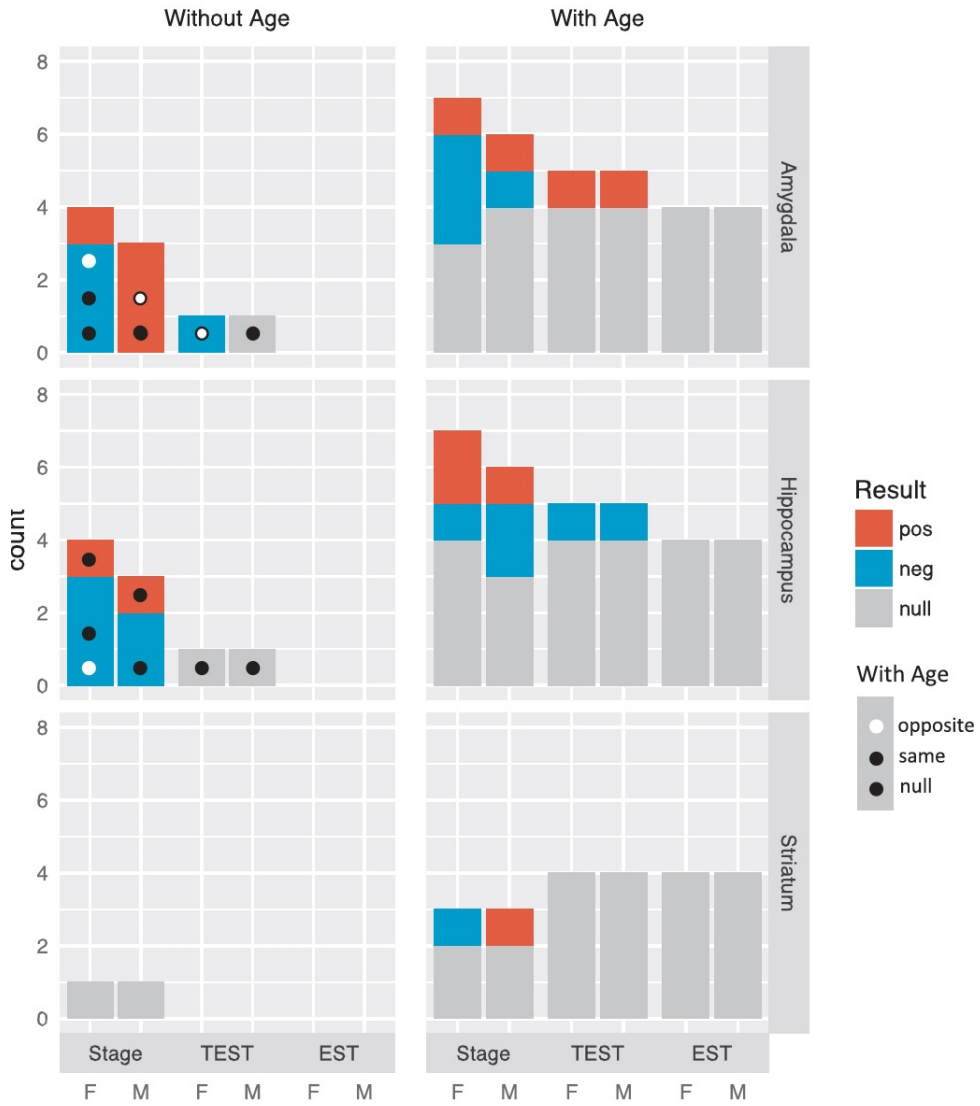
positive
negative
null

Puberty and regional cortical GM (cross-sectional)



- Consistent decreases in frontal, temporal GM with self-report and hormonal indices of puberty (timing)

Puberty and subcortical GM



Puberty and WM volume/density, FA, & MD

A)	Volume/density	
	Without age	With age
Pubertal stage		
Chavarria et al., 2014	CC	
Pfefferbaum et al., 2015	global	
Perrin et al., 2009	all lobes	
Peper et al., 2009b		occipital
Pangelinan et al., 2016		CST
Testosterone		
Paus et al., 2010	global	
Herve et al., 2009	CST	CST
Perrin et al., 2008	global	
Peper et al., 2009c		global/regional
Pangelinan et al., 2016		CST
Estradiol		
Paus et al., 2010		global/regional

B)	FA		MD	
	Female	Male	Female	Male
Pubertal stage				
Bava et al., 2012	CST, SCR		ILF, forceps major	
Herting et al., 2012	insula			
	superior front	superior front		
Menzies et al., 2015		SLF, ILF, CLT, CST		SLF, ILF, CLT, CST
Testosterone				
Barendse et al., 2018				
Herting et al., 2012	precentral	superior temp, front, angular gyrus, thalamus, CC, IC		superior front
Peper et al., 2015			subcortico-temp	
Menzies et al., 2015 *				SLF, ILF, CLT, CST
Estradiol				
Herting et al., 2012	angular gyrus, IC, SLF	Cingulum, superior front, precuneus, thalamus		
Peper et al., 2015				
Menzies et al., 2015 *				SLF, ILF, CLT, CST

positive
negative
null

Summary of Vijayakumar et al. (2018)

- PFC is among the most consistently associated regions with pubertal maturation (superior/inferior frontal and anterior cingulate cortices)
- Amgydala and hippocampus structure are associated with pubertal stage (varies by sex); ventral striatum activation to reward receipt associated with pubertal stage and testosterone
- Functional activation patterns are still somewhat unclear (see also Dai & Scherf, 2019)
- Longitudinal pubertal and hormonal processes, rather than absolute stages/levels, more likely to be informative

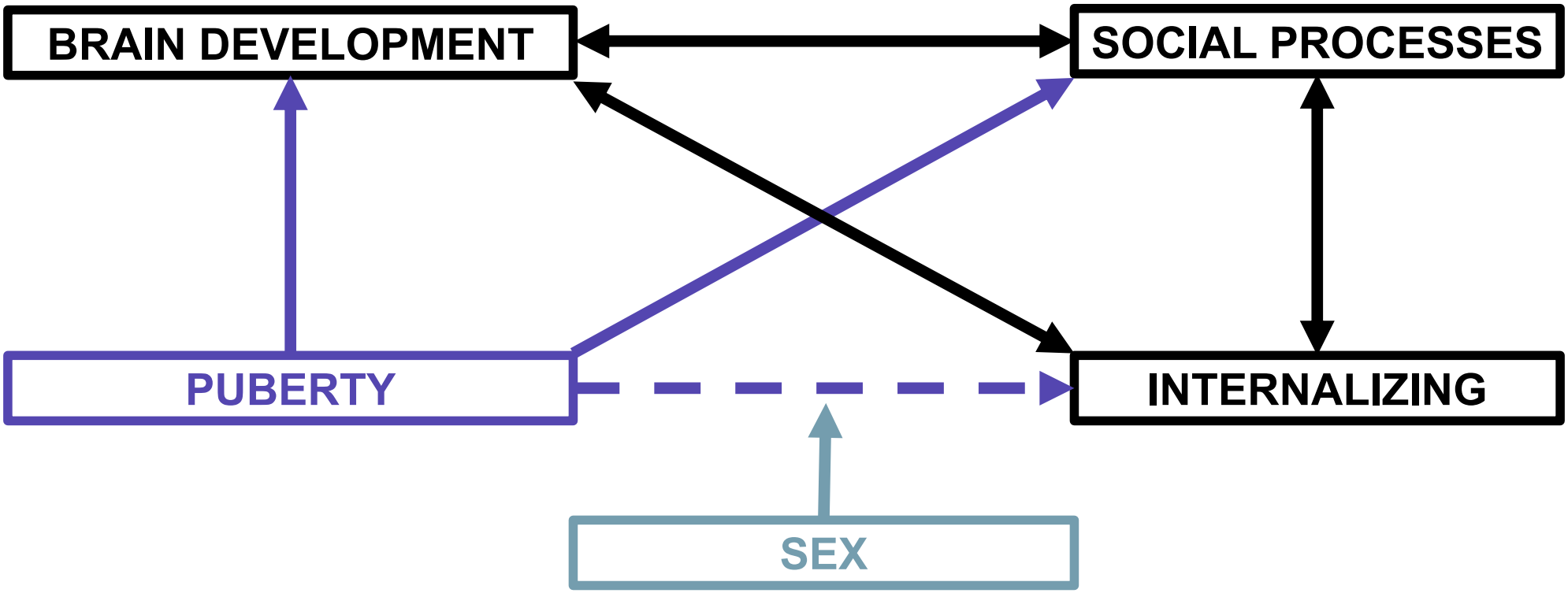
Emerging evidence brain development *mediates* puberty → mental health link

https://medicine.unimelb.edu.au/research-groups/psychiatry/melbourne-neuropsychiatry-centre/social-affective-neurodevelopment-sand

- Larger pituitary volumes mediated relationships between:
  - Early pubertal timing and increased depressive symptoms (Whittle et al., 2012)
  - Greater DHEA levels and increased social anxiety symptoms (Murray et al., 2016)
- Larger hippocampal volume mediated link between greater T levels and increased depressive symptoms in girls (Ellis et al., 2019)
- Weaker activation in posterior insula elicited by happy emotional expressions mediated link between greater DHEA levels and increased externalizing symptoms (Whittle et al., 2015)
- Amygdala connectivity during emotion processing mediated link between early adrenarcheal timing and increased anxiety symptoms (Barendse et al., 2019)

Heuristic Model

impact of puberty on adolescent mental health



Pfeifer & Allen (2021), *Biol Psychiatry*

II. Early Life Stress

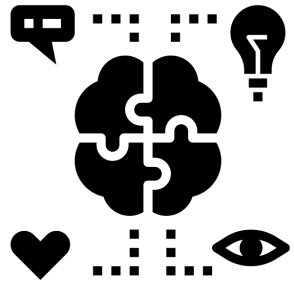
Early Life Stress (ELS) and Mental Health

- Conceptualizations of ELS have moved from cumulative risk to dimensional approaches that include threat, deprivation, and unpredictability (McLaughlin & Sheridan, 2016; Ellis et al., 2009)
- ELS linked to ~45% of all child-onset mental health disorders, and ~30% of all adult-onset ones (McLaughlin et al., 2010)
- Body and brain adaptations to ELS can have negative long-term consequences (Herzberg & Gunnar, 2020)
  - Drives and thereby remodels HPA axis functioning
  - Deviations from healthy levels of basal cortisol can impact behavior & brain structure/function

Accelerated Maturation/Stress Acceleration

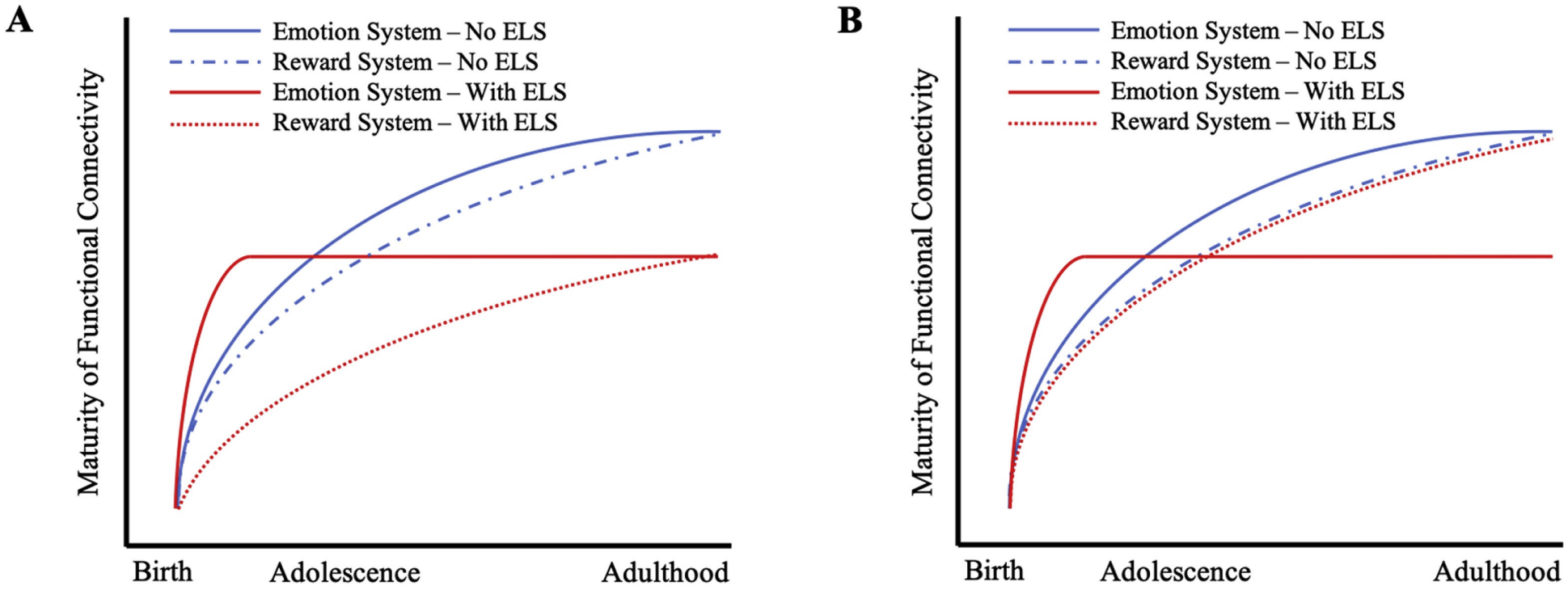
- Psychosocial stress accelerates biological maturation, including early pubertal development (Belsky et al., 1991; Del Giudice et al., 2011)
- ELS-advanced pubertal timing associated with developmental of psychopathology (Colich et al., 2019)
- ELS may cause premature maturation of emotion-related brain circuitry (Callaghan & Tottenham, 2016)

ELS and *human* brain development



- Structure
  - Differences in thickness/volume of amygdala, hippocampus, medial and lateral PFC, and superior parietal cortex
- Function
  - Increased amygdala response to/enhanced processing of negative emotions
  - Blunted VS response and impaired processing of rewards/positive emotions
  - Mixed effects in lateral PFC
- Emerging evidence in relation to mental health:
  - Reward-related responses in VS mediated link between community disadvantage and anxiety (Marshall et al., 2018)
  - VS-mPFC connectivity explained ~ 10% of variance in ELS-internalizing link (Hanson et al., 2018)
  - See also Marusak et al., 2015, 2017; Fareri et al., 2017

Possible developmental trade-off (and implications for timing of assessments)

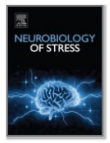


Herzberg & Gunnar (2020)

How does ABCD do it?

ELSEVIER

Neurobiology of Stress
Volume 10, February 2019, 100157



Stress exposures, neurodevelopment and health measures in the ABCD study

Elizabeth A. Hoffman [a] [1] ✉, Duncan B. Clark [b], Natalia Orendain [c], James Hudziak [d], Lindsay M. Squeglia [e], Gayathri J. Dowling [a]

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https://doi.org/10.1016/j.ynstr.2019.100157

Abstract

The Adolescent Brain Cognitive Development (ABCD) Study, a large, longitudinal study of brain development and child health, is uniquely positioned to explore relationships among stress, neurodevelopment, and

Adverse Childhood Experiences (ACEs) Domain[a]	ABCD Baseline Assessment (Parent, Youth)	Description
Abuse:		
Emotional abuse	Not assessed	N/A
Physical abuse	Family Environment Scale (parent and youth); KSADS-5, PTSD module (parent)	Social-environmental characteristics of family function; youth exposure to and experience of trauma
Sexual abuse	KSADS-5, post-traumatic stress disorder module (parent)	Youth exposure to and experience of trauma
Household Challenges:		
Mother treated violently	KSADS-5, PTSD module (parent)	Youth exposure to and experience of trauma
Household substance abuse	Family History Assessment; Adult Self-report (parent)	Family history of psychopathology and substance use; criminal behavior
Mental illness in household	Family History Assessment; Adult Self-report (parent)	Family history of psychopathology and substance use; criminal behavior
Parental separation or divorce	Demographics Survey (parent)	Family demographics, including race, gender, family structure, SES, education and occupation
Criminal household member	Family history Assessment (parent)	Family history of psychopathology and substance use; criminal behavior
Neglect:		
Emotional neglect	CRPBI Acceptance Subscale (youth)	Youth perception of caregiver acceptance
Physical neglect	Parental Monitoring (youth); Demographics Survey (parent)	Youth perception of parental supervision; family demographics (economic hardship, e.g., food insecurity)

Conclusions

- A multiverse of ways to measure these mechanisms
- For both puberty and early life stress, method and timing of asessments is key!
  - Essential to match these with your research question
- ABCD may offer opportunities to test path models whereby earlier developmental effects (puberty, ELS, environment, parenting) launch cascading relationships between brain, behavior (social, emotional, motivational, regulatory), and mental health