



Puberty and Neuroendocrine Changes in Adolescents

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Objectives

- 1 Briefly describe what we know about neuroendocrine changes and risk taking,
- 1 Discuss the progress of sex-hormone research in understanding risk taking, and
- 1 Describe how understanding neuroendocrine changes can inform prevention of risk taking.



What is puberty?

- 1 Puberty [L. *pubertas*, from *pubes*, *puber*, of ripe age, adult]
- 1 Defined as: “the state of physical development at which time persons are first capable of begetting or bearing children”.



Brain- Neuroendocrine- Puberty

- 1 Brain Development is responsible for:
 - Reproductive maturation,
 - Physical Growth, and
 - Behavior changes at puberty



Brain Maturation and Reproduction

- 1 *Hypothalamus* is responsible for neurosecretory factors and/or hormones changes at puberty,
- 1 All of which modulate:
 - somatic growth,
 - development of the primary and secondary sex characteristics, and
 - alterations in the endocrine system.



Primary Neuroendocrine Event

- 1 Reactivation of the hypothalamic-pituitary-gonadal (HPG) axis, specifically, GnRH:
 - Induces and enhances the progressive secretion of ovarian and testicular sex hormones (testosterone and estrogen)
 - Is responsible for profound morphological changes (secondary sex characteristics, height and weight).

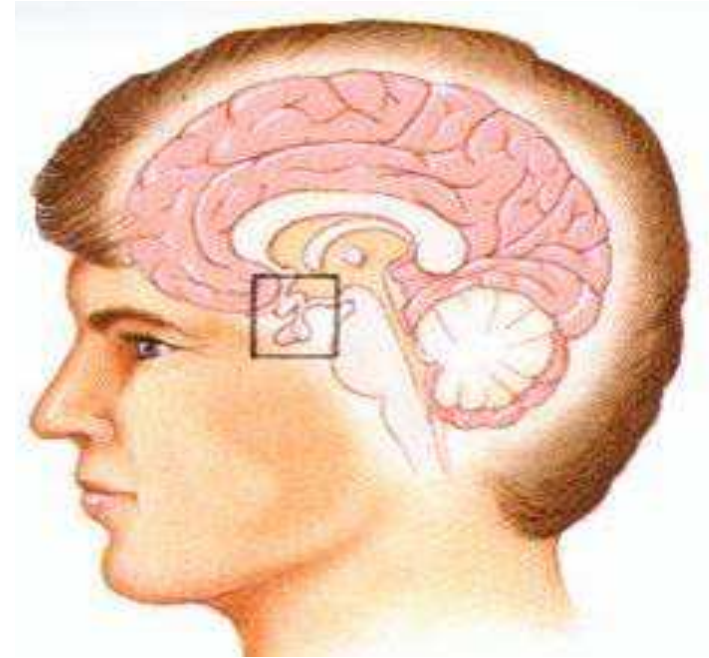


HPG axis

Hypothalamus

Pituitary

Gonads
Ovaries and
Testes



What are the specific precipitating signals for the onset of puberty?

- 1 Genes: polygenetic trait (KISS peptin?)
- 1 Hypothalamic neuroendocrine
 - characterized by pulsatile release of gonadotropin releasing hormone (GnRH).
- 1 Environmental factors, obesity, family influences?



Why is puberty important in risk taking?

- 1 Risk taking increases during the pubertal transition.
- 1 Sex hormones (i.e. testosterone) have been strongly implicated in risk taking behavior.



Puberty

- 1 Puberty is considered to awaken the brain to both pleasure and risk.
- 1 This awakening frequently takes the form of experimentation with drugs and sex.



First Generation Hormone-Behavior Studies

- 1 Hypotheses were based on animal model study findings:*
 - Hypothesis: Higher levels of gonadal hormones (estrogen and testosterone) are associated with aggressive behavior.



Aggressive Behavior and Hormone Profile

- 1 *Adolescent* model studies:
 - Higher levels of gonadal hormones (estrogen and testosterone),
 - were related to aggressive behavior (Susman et al 1987,1990).
 - Sometimes!



Timing of Puberty

- 1 Healthy-adolescent individual differences in timing
- 1 Adolescents with endocrine disorders:
 - Genetic
 - Hypothalamic
 - Hypopituitary
 - Hypogonadal
 - Constitutional Delay



Timing of Puberty

- 1 Timing of puberty (earlier and later) is associated with virtually every risk behavior.
- 1 Early timing is detrimental for girls.
- 1 Boys: ??





Establishing causality

- 1 How does one establish causality when considering the role of hormones in risk taking and timing of puberty?



Natural Experiment: Delayed Puberty

- 1 What is the effect of administering sex steroids for treatment:
 - testosterone
 - estrogen
- 1 On aggression, behavior problems, cognition, and competencies in delayed puberty adolescents?



Hershey Study: Randomized clinical trial

- 1 Sample: Adolescents with delayed puberty
- 1 Diagnoses:
 - gonadal disorder (e.g., Turner's syndrome)
 - gonadotropin deficiency
 - constitutional delay.



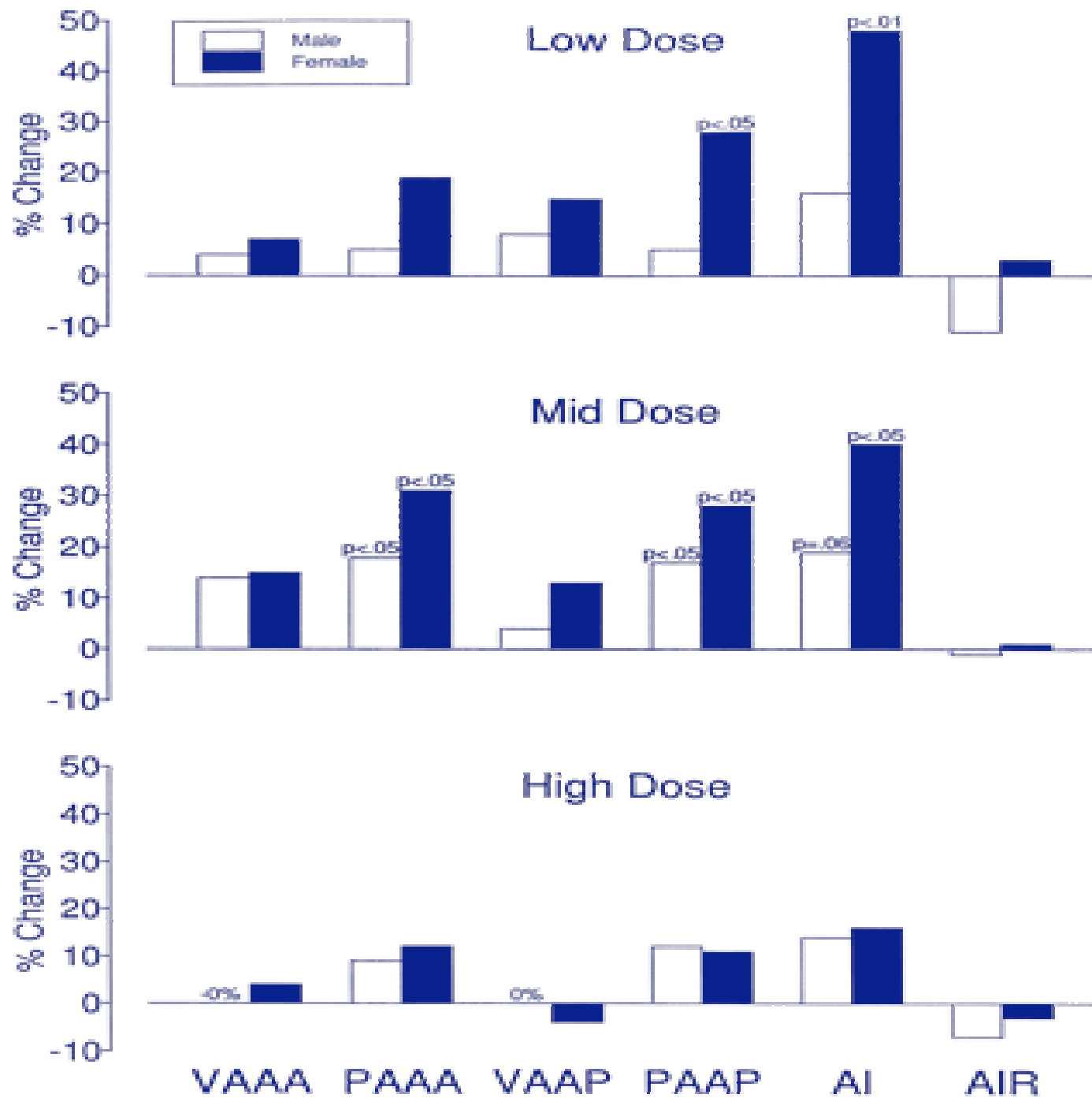


Design

Visit	1	2	3	4	5	6	7	8
Arm X	Baseline	Placebo	Low	Placebo	Middle	Placebo	High	Placebo
Arm Y	Baseline	Low	Placebo	Middle	Placebo	High	Placebo	High*

* High dose for permanently hypogonadal subjects, repeat placebo for constitutionally delayed subjects.





Three Conclusions

- 1 Sex hormones have a significant effect on increasing aggression in delayed puberty adolescents.
- 1 Girls responded to a *low* (*early puberty*) dose of estrogen whereas boys respond to a *medium* (*mid puberty*) dose of testosterone.



Conclusions cont.

- 1 In adolescents with a diagnosis of constitutional delayed puberty, some did not respond to the replacement therapy, or responded very slowly.
- 1 Do contextual factors prevent the onset of puberty? Family stress?



Do the neuroendocrine changes affect structural brain changes?

- 1 The volume of white matter increases with age slightly in girls and steeply in boys.
- 1 Androgen receptor (AR) is involved in mediating the effect of testosterone on white matter (Paus, et al., 2008)



Brain and testosterone

- 1 Testosterone related increases in white matter volume was stronger in male adolescents with **lower** numbers of CAG repeats in the androgen receptor (AR) gene (Paus et al., 2008)
- 1 Lower CAG indicates higher testosterone activity





Paus et al cont.

- 1 White matter change not related to myelination but to axon caliber.
- 1 Are there behavioral risks associated with the rate of growth in white matter?
- 1 Is rate of change in white matter related to timing of puberty



Testosterone and Substance Use (Tarter et al., 2007)

- 1 Testosterone promotes social dominance.
- 1 Social dominance is associated with norm-violating behavior,
- 1 Which predisposes to substance use.

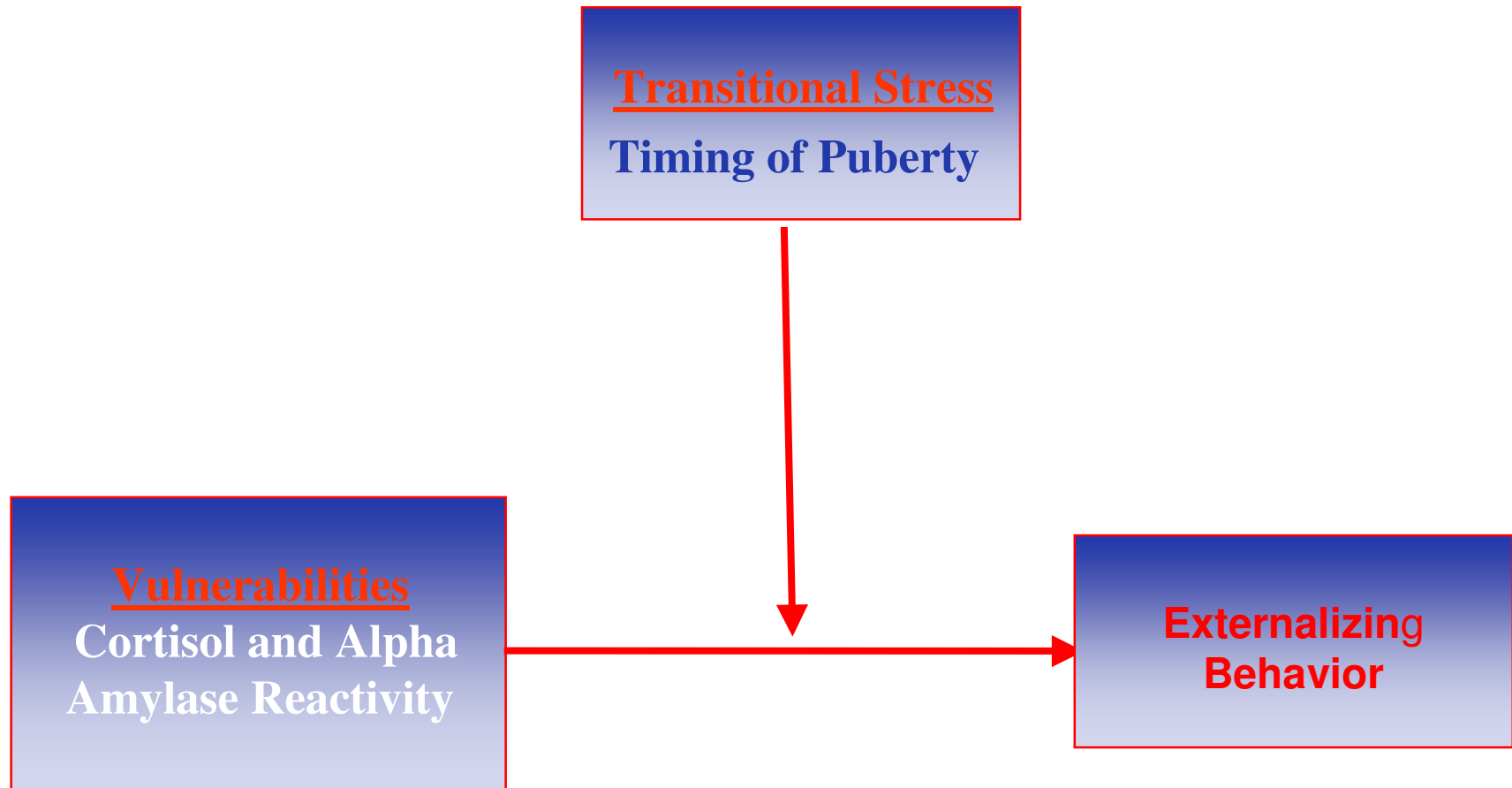





Timing of Puberty

- 1 What are the mechanisms involved in moderating timing of puberty and risk taking behavior?







What is the stress level of the context in which adolescents find themselves?

Does timing of puberty affect the psychobiology of stress?

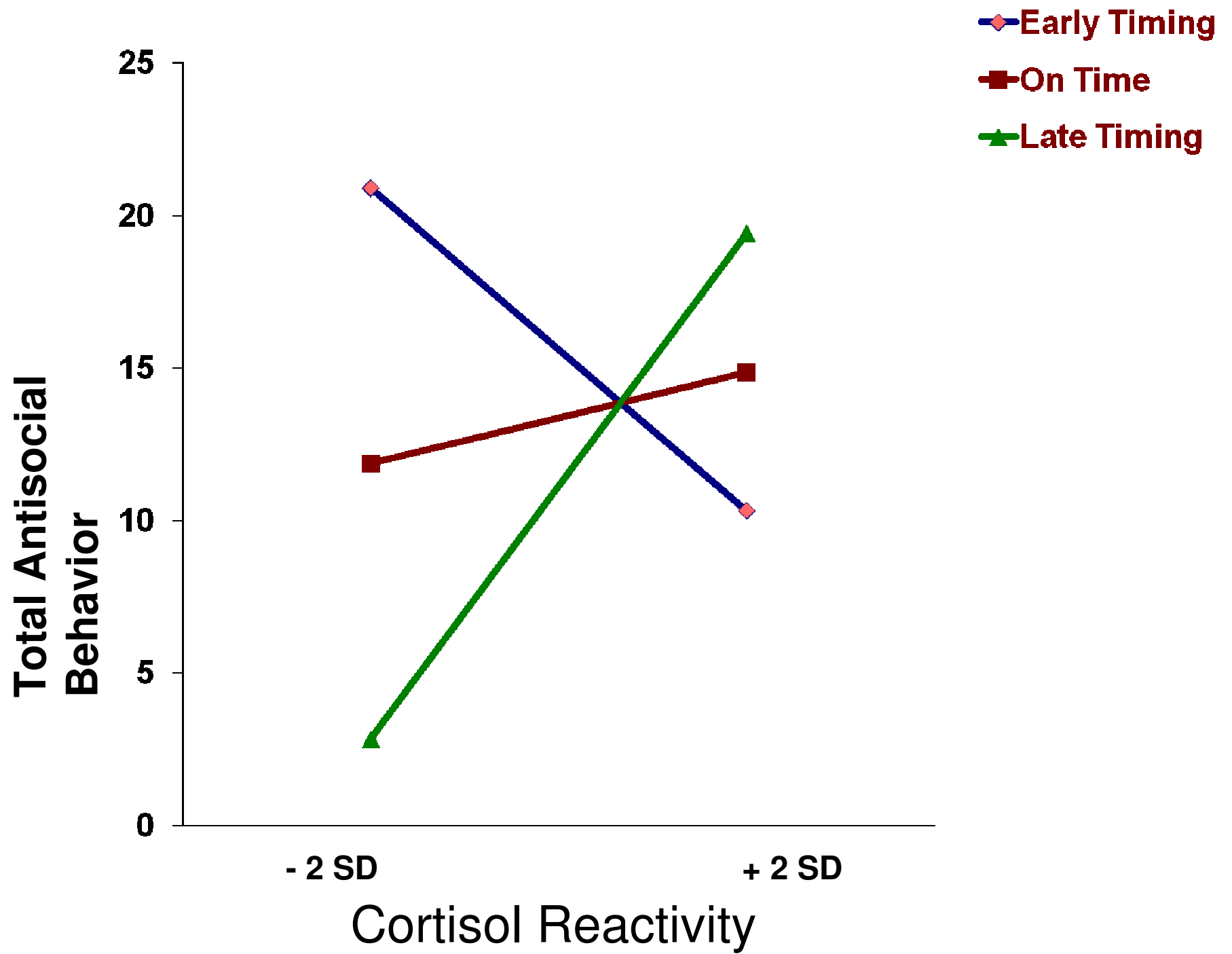


Vulnerability Biomarkers

1 HPA: Cortisol

- Secreted by the adrenal cortex
 - » The “ultimate” stress hormo





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Converging lines of evidence

- 1 Puberty is a sensitive period for steroid-dependent brain organization.
- 1 Testosterone linked to dominance and aggressive behavior.
- 1 Testosterone may act as a permissive signal for risk taking.



Implications of Neuroendocrine Changes

1 Prevention:

- Increase parental awareness of the importance of puberty as an at-risk transition.
- Based on the neuroendocrine changes that occur in early adolescence, prevention efforts will be earlier than usually the case and will be gender specific.





The Forgotten Adolescent

Did the adolescent get lost in the
multiple contexts of
development?



Neuroendocrine change and Contextual Issues

- 1 Adolescents influence the contexts in which they develop.
- 1 Adolescents are “producers” of their own development.





1 The End

