



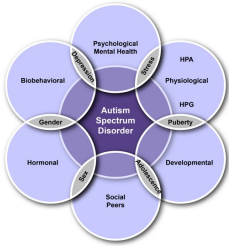
Trends in Research:
Overlooked areas in
Autism, Females,
Adolescence/Puberty and
Mental Health

Blythe A. Corbett, Ph.D.
James G. Blakemore Chair and
Professor, Vanderbilt University
Medical Center
Cyprus 2024

1

Outline

- Autism Spectrum Disorder
- Developmental: Adolescence, Puberty
- Physiological: HPA and HPG
- Psychological: Mental Health
- Biobehavioral: Interactions
- Hormonal: Sex and Gender
- Social: Peers



2

Autism Spectrum Disorder (ASD) DSM-V Criteria

- **Social Communication**
 - Social emotional reciprocity
 - Nonverbal communication
 - Developing and maintaining relationships
- **Restricted Repetitive Patterns of Behavior, Interests or Activities**
 - Stereotyped or repetitive movements
 - Insistence on sameness
 - Restricted, fixed interests
 - Hyper- Hypo-reactivity to sensory stimuli

3

Developmental

A Venn diagram with three overlapping circles. The largest circle on the left is purple and labeled 'Autism Spectrum Disorder'. The circle on the top right is light blue and labeled 'Puberty'. The circle on the bottom right is light blue and labeled 'Developmental'. The intersection of all three circles is shaded in a darker blue.

4

Adolescence

- Adolescence is a time of significant psychological, social, emotional and hormonal changes (Spear, 2000; Steinberg, 2005) with greater emphasis on psychosocial development including peer relationships.
- Characterized by transitions and changes in identities as youth experiment and explore *who* they are, *what* they like, and *how* this interacts with their environment or others (Katz-Wise et al., 2023).
- Stages include early (10-14 years), middle (15-17 years) and late adolescence/young adulthood (17 – 24).

5

Puberty

Puberty refers to biological maturation contributing to significant changes in morphology, cognition, emotion regulation and physiological stress that leads to reproductive capacity and psychosocial development (Spear, 2000; Steinberg, 2005).

External Development: The emergence of secondary sexual characteristics distinguishing the sexes signals the onset of puberty, involving breast development (thelarche) in females and genitals (gonadarche) in males and pubic hair (pubarche) in both sexes.

Internal Development: Endocrine axis orchestrating gonadal steroid production and adrenal androgen production.

6

Early Onset Risks

Deviations in pubertal timing can enhance the risk for mental health problems (Ge, 2009; Graber, 1997; Kaltiala-Heino, 2003; Negriff, 2011; Waylen, 2004).

Increased risk factor in females (Marceau, 2014; Mendle, 2007) for depression (e.g., Angold, 2003; Conley, Ge, 2001; Lewelllyn, 2012; Rierdan, 1991), suicidality (Graber, 1997) and anxiety (Patton, 1996).

These mental health conditions have a higher prevalence in adolescents with ASD (e.g., Gotham, 2015; Kuusikko, 2008; White, 2009).



7

Puberty & ASD

Limited research on adolescence and puberty (Picci, 2015), even though autistic individuals show poor adaptation to developmental transitions (Taylor, 2010; 2017).

During puberty, some improvements have been found (e.g., Anderson, 2011; Brown, 1969; Rutter, 1970; Seltzer, 2004).

Social withdrawal often intensifies (Anderson, 2011) and 1/3 of youth experience significant psychosocial problems (Billstedt, 2005; Gillberg, 1987).

Onset of menses often accompanied by challenges with emotion regulation (Burke, 2010; Obaydi, 2008) and heightened sensory experiences (Hamilton, 2011; Steward, 2018).

8

Pubertal Measurement -Tanner Staging

A brief, standardized physical exam conducted by trained study physicians developed by Marshall and Tanner (1969, 1970).

Two measures with 5 stages:

Genitals (G1-G5 for males) and **Breasts** (B1-B5 for females) (GB stage)

Pubic hair (P1-P5 for both genders) (PH stage)

For our studies we use visual inspection only to be consistent with original Tanner staging and to maximize participation.



9

HHS Public Access
 Author manuscript
Autism Res. Author manuscript; available in PMC 2023 October 01.

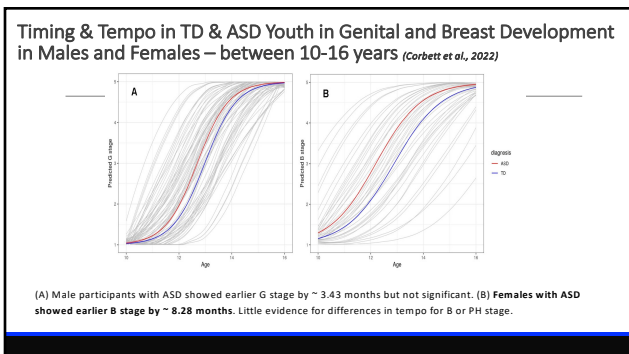
Published in final edited form as:
Autism Res. 2022 October ; 15(10): 1894–1908. doi:10.1002/aur.2786.

Examination of Pubertal Timing and Tempo in Females and Males with Autism Spectrum Disorder compared to Typically Developing Youth

Blythe A. Corbett, Ph.D.^{1,2,3}, Rachael A. Muscatello, Ph.D.¹, Ahra Kim, M.P.H.⁴, Simon Vandekar, Ph.D.⁴, Sara Duffus, M.D.⁵, Sloane Sparks, DNP, PMHNP¹, Yasas Tanguturi, M.D.¹

Years/Ages Y1 = aged 11-13; Y2 = aged 11-14; Y3 = aged 12-15
 Timing is the onset of puberty
 Tempo is the pace or progression through puberty

10




11

Pubertal Timing Summary and Considerations

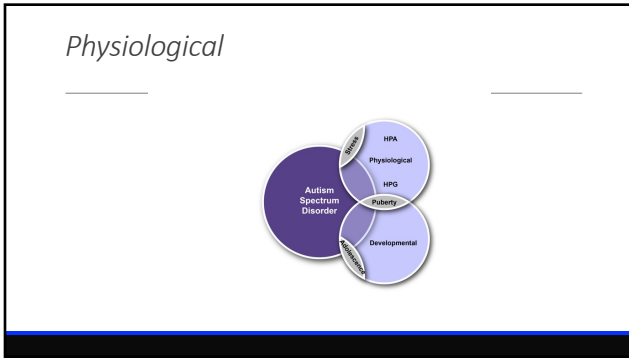
Females with ASD evidence advanced pubertal onset relative to TD females and ASD males.

Pubertal onset sets into motion a cascade of events which may magnify and further complicate an already vulnerable trajectory, especially in females.

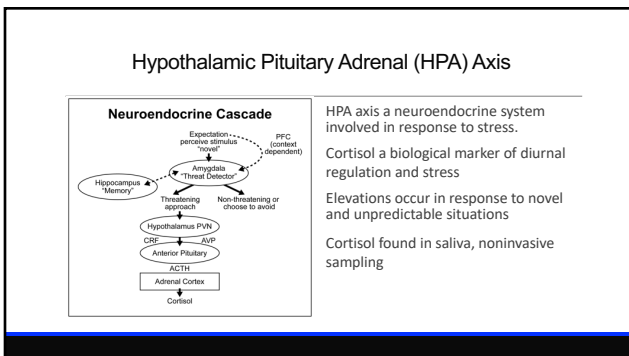
Early onset risks may involve psychosocial (e.g., peer relations (Graber, 2004; Hamilton, 2014), biological (e.g., hormones, Apter, 1983; Dahl, 2004) and environmental effects (e.g., paternal absence, low SES (Bogaert, 2005; Ellis, 2000; Mendle, 2007; Obeidallah, 2000)).



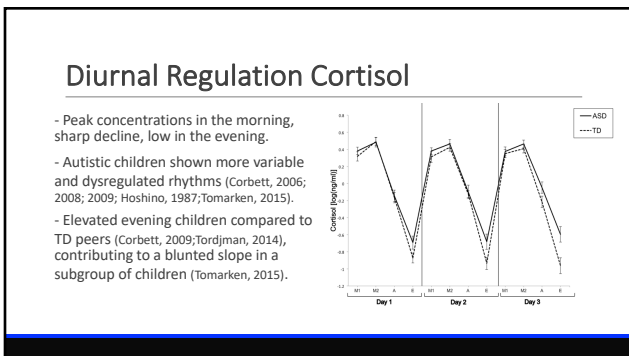
12



13



14



15

HPA Axis and Adolescence

- The adolescent period is marked by significant physiological changes in the regulation and responsivity of the HPA axis.
- Developmental changes result in elevations in diurnal cortisol levels (Barra, 2015) and higher cortisol in response to perceived stressors (Gunnar, 2009).

16

Development and Psychopathology (2023), 1-12
doi:10.1017/S0954579423000810



Regular Article

The developmental trajectory of diurnal cortisol in autistic and neurotypical youth

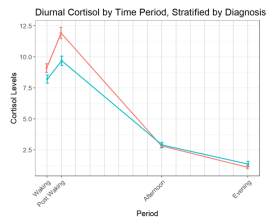
Blythe A. Corbett^{1,2,3}, Trey McGonigle⁴, Rachael A. Muscatello¹, Jinyuan Liu⁴ and Simon Vandekar⁴

Investigating diurnal cortisol by examining:

- Aim 1) **Diagnosis:** cortisol expression longitudinally over the pubertal transition between autistic and neurotypical youth
- Aim 2) **Development:** the trajectory of diurnal cortisol and the unique contributions of age vs. puberty
- Aim 3) **Sex:** potential sex differences

17

Mean diurnal cortisol levels over the course of the day stratified by Diagnosis

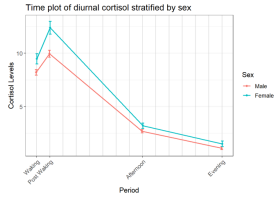


As hypothesized, autistic compared to TD youth demonstrate a shallower diurnal slope and elevated evening cortisol.

Differences were in the context of higher cortisol and flatter rhythms based on age and pubertal development.

18

Mean diurnal cortisol levels over the course of the day stratified by Sex



Sex-based differences emerged - females in both groups had higher cortisol, flatter slopes, and higher evening cortisol than males.

HPA maturation is impacted by age, puberty, sex, as well as an ASD diagnosis.

19

Psychological



20

Adolescence and Mental Health

- In general population, half of people who will suffer from mental illness will have their onset by 14 years of age (Kessler et al., 2005).
- Adolescence is a pivotal transition for youth with ASD, a condition characterized by difficulty with social competence and poor adaptability to change, including developmental transitions.
- The timing of the release of pubertal hormones contributes to individual differences in sex-biased psychopathological conditions, including depression.

21

> Res Autism Spectr Disord. 2020 Sep;77:101613. doi: 10.1016/j.rasd.2020.101613. Epub 2020 Jul 17.

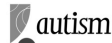
Higher depressive symptoms in early adolescents with Autism Spectrum Disorder by self- and parent-report compared to typically-developing peers

Jessica M Schwartzman¹, Blythe A Corbett^{1,2}

- Depressive symptoms are higher in male and female early adolescents with ASD than TD peers based on self-report.
- Parents of autistic adolescents also report higher depressive symptoms.
- Screening and intervention for depressive symptoms in ASD should occur during early adolescence.

22

Original Article



Diagnostic- and sex-based differences in depression symptoms in autistic and neurotypical early adolescents

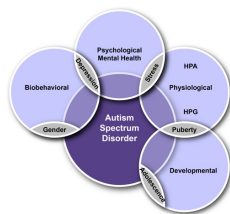
Jessica M Schwartzman¹, Zachary J Williams^{1,2} and Blythe A Corbett^{1,2}

Autism
1-14
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journalsPermissions
DOI: 10.1177/14234415211025895
journals.sagepub.com/home/aut
SAGE

- Based on sample of 212 adolescents, diagnosis of ASD and female sex pose elevated risks for depression during adolescence.
- Depressive symptoms related to interpersonal problems, negative self-esteem, and beliefs of worthlessness, suggesting intervention targets.

23

Biobehavioral



24

Corbett et al. *Molecular Autism* (2024) 15:19
<https://doi.org/10.1186/s13229-024-00600-w> Molecular Autism

RESEARCH Open Access

Trajectory of depressive symptoms over adolescence in autistic and neurotypical youth

Blythe A. Corbett^{1,2,3*}, Rachael A. Muscatello^{1,2}, Trey McGonigle⁴, Simon Vandekar⁴, Christina Burroughs¹ and Sloane Sparks¹

25

A Predicted Total CDI T-Score by Age

B Predicted Total CDI T-Score by GB Stage

Diagnosis: TD (red line), ASD (teal line)

ASD group showed elevated depressive scores in early adolescence/puberty decreased during middle adolescence/puberty ($p < 0.001$).

TD group showed opposite trend increase in depression symptoms over development.

Females higher than males in both groups ($p = 0.001$).

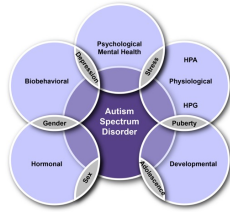
26

ASD and Depression Summary

- Results reveal significant differences in autistic youth showing higher depression symptoms earlier in development (age, pubertal stage), then decreasing during later in development
- TD youth show the opposite pattern.
- Sex differences were observed in both groups, females showing higher symptoms of depression.
- Findings suggest a period of quiescence in depressive symptomatology that may be influenced by biopsychosocial factors.

27

Hormonal



28

Testosterone and ASD

The etiology of ASD is uncertain, imbalances in hormones, such as testosterone, may modulate the autism phenotype (e.g., Baron-Cohen, 2006). Differences in fetal and postnatal testosterone have been reported, there is limited literature regarding testosterone variations during adolescence in ASD.

29

Muscibelli et al. Molecular Autism (2022) 13:17
https://doi.org/10.1186/s12272-022-00115-4

Molecular Autism

RESEARCH Open Access

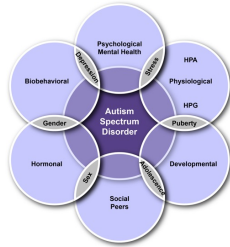
Salivary testosterone in male and female youth with and without autism spectrum disorder: considerations of development, sex, and diagnosis

Rachael A. Muscibelli¹, Emma Rafatjoo², Karan K. Mirpur², Ahra Kim³, Simon Vandekar³ and Rhyne A. Corbett^{1,4*}

Youth with ASD show elevated testosterone compared to TD peers ($p < 0.05$).
 Distinct developmental slopes for males/females ($p < 0.05$).
 At younger ages, females had higher testosterone, until ~ 11.5 years when levels plateau. Male testosterone rapidly increases and surpass females.

30

Social



31

Overarching Summary of ASD Findings

Autistic females enter puberty earlier than TD females and ASD/TD males, putting them at risk for psychological, physical and social challenges.

Higher rate, earlier onset of depression in ASD, especially autistic females.

Need to comprehensively measure psychological variables based on self-report, parent-report and clinical-report.

Adolescent/pubertal development is not necessarily linear, we need to identify factors of risk and resiliency to elucidate and support this dynamic transition.

32

Model

- Autism Spectrum Disorder
- Developmental: Adolescence/Puberty
- Physiological: HPA and HPG
- Psychological: Mental Health
- Biobehavioral: Interactions
- Hormonal: Sex and Gender
- Social: Peers



33

Acknowledgements

We thank the children and families who participate in our research!

Current Funding

NICHD R01 107695

NIMH R01 111599-061A

NIMH R33 120149

Previous Relevant Funding

NIMH R01 114906

NIMH R01 111599

NIMH R34 MH097793

NIMH R01 MH085717

34

Thank you!



35