Brain And Behavioral Development In Klinefelter Syndrome

Allan L. Reiss, M.D.
Stanford University
Goals of this talk

- Understand our current state of knowledge regarding brain, cognitive-behavioral and social-emotional development in Klinefelter syndrome
- Learn current methods for assessing brain structure and function in Klinefelter syndrome
- Learn how a “precision medicine” approach could improve specificity and effectiveness of treatment in Klinefelter syndrome
- Describe new research at Stanford
- Q & A
Pre-Talk (Fun) Pop Quiz – 6 Questions

■ Genetic variations in human beings are very rare ...
  - True or False?

■ More boys with Klinefelter syndrome are born every year in the U.S. than boys with Down syndrome ...
  - True or False?

■ Brain imaging research is primarily a technique to “read” people’s minds ...
  - True or False?

■ “Precision medicine” allows doctors to provide effective and targeted treatment based on an individual patient’s genetic, medical and environmental information ...
  - True or False?
Nature Versus Nurture?

Nature AND Nurture

DNA

AND

Child playing

Mother with child
Is the Human Brain Dimorphic?

- What do you think? Yes? No?

Cahill et al. Scientific American, 2005
Klinefelter Syndrome – the Basics

■ Due to an “extra” X chromosome in a male (47XXY)
■ Most common sex chromosome condition
  - (1/500-1000 males)
■ Characteristics can include testicular insufficiency, tall stature, gynecomastia and impaired spermatogenesis
  - Often requiring testosterone therapy
■ Increased risk for cognitive-behavioral and social-emotional features:
  - Language problems
  - Executive function problems and ADHD symptoms
  - Social-emotional problems
  - Depressive symptoms
■ Many associated ”DSM” diagnoses (though of questionable importance aside from obtaining resources)
Cognitive-Behavioral and Social-Emotional Issues in KS

- Relative weaknesses in attention, verbal memory, inhibition and motor function compared to typically developing age-matched boys 4-17 years
- Higher anxiety and depressive symptoms, greater social problems compared to typically developing age-matched pre-pubertal boys
- More problems with executive function, social-emotional function and depression compared to typically developing age-matched pre-pubertal boys
- Speaks to importance of early identification and treatment!

**Figure.** Reduced executive (BRIEF, BASC2 attention), social (SRS) and emotional (BASC2 depression) function in boys with KS relative to age-matched TD boys. Lower scores are better.
Puberty and adolescence mark a transitional period between childhood and adulthood of immense behavioral and physical change.

Although the terms “puberty” and “adolescence” are frequently used interchangeably, to specialists, puberty refers to a distinct developmental period within adolescence during which complex neuroendocrine processes culminate in gonadal maturation.

Changes in gonadal hormones (i.e., estrogen, testosterone) occurring during puberty exert a powerful effect on brain circuits, including circuits underlying cognitive and emotional function.

These effects occur via permanent modification to brain structure (e.g., change in neuronal number, myelination or dendritic branching) – so-called “organizational effects”, and (b) through temporary modification of brain circuits (e.g., activation of neural systems that underpin reproductive behaviors in young adulthood) – termed “activational effects”
Puberty and Brain Development

- Until recently, researchers believed that fundamental organizational effects induced by gonadal hormones occurred only early in life, during perinatal development. It is now clear that this process continues at puberty, when gonadal hormones spike for a second time.

- This revised understanding of the brain has sparked a reconceptualization of puberty as a second “critical period” in brain development.

- Emphasizes the importance of understanding and optimizing pubertal hormone levels in persons with KS!

![Testosterone changes through the lifespan.](image)
Testosterone Replacement Therapy (TRT)

- Standard treatment for KS consists of testosterone replacement therapy (TRT) beginning at or around puberty, to correct testicular insufficiency and promote the development of age-appropriate secondary sexual characteristics
  - In actual clinical settings, much variation in whether to treat as well of timing of TRT

- There is little information as to whether TRT improves cognitive-behavioral or social-emotional outcomes in KS when individuals are treated in the peri-pubertal period over time

- Recent information suggests low doses of androgen in young, pre-pubertal children with KS (4-12 years) may improve some outcomes
  - Ross et al., J Pediatrics 2017 (cognitive-behavioral – visuo-motor, social-emotional)
  - Davis et al., J Pediatrics 2017 (cardiometabolic – reduced % body fat, but ± lipids)
Other Things to Know About Testosterone

■ Several small studies suggest that TRT has a beneficial effect on mood and self-esteem in hypogonadal men (including KS)

■ Testosterone may “protect” against or even treat depression

■ Testosterone (androgen) receptors are found throughout the brain, but particularly in regions underlying sexual behavior, emotion processing and learning/memory (e.g., hypothalamus, amygdala, hippocampus, cortex)
  - Effects may be different depending on developmental period (adult vs childhood)

■ Testosterone levels can be measured in the blood (and maybe saliva)
  - Associated with variation in brain circuits underlying cognitive-behavioral and social-emotional function in typical adolescent development
Importance of Brain Imaging in KS Research
Structural Imaging – Snapshot of Anatomy
Diffusion Weighted Imaging – Snapshot of Wiring/Connectivity
Functional Imaging (fMRI)
Another Interesting Imaging Modality – fNIRS
Brain Differences in KS at Baseline And In Response To Testosterone
Brain Imaging Results - Summary

- Smaller volume of the amygdala
  - Involved in processing faces, emotions, social cues
- Smaller volume of hippocampus
  - Involved in learning and memory
- Smaller volume of insular cortex
  - Involved in interoception, theory of mind
- Larger volume of sensorimotor and posterior cortical regions
  - Related to developmental compensation and relative strengths in visual-spatial ability?
- Papers
  - Patwardhan et al. Amer J Med Genet, 2002
  - Hong et al. J Neuroscience, 2014
Retrospective Look at Testosterone Effects in Adults with KS

- 20 subjects, 10 with KS
- 5 in KS group received testosterone
- Patwadhan et al., Neurology 2000
Low Dose Oxandrolone Affects Hippocampal Volume in Pre-pubertal Boys with KS

Foland-Ross et al., *Psychoneuroendocrinology*, 2019
How Can We Learn More About Hormonal and Environmental Influences in KS?

- Very little data available about the effect of hormone intervention in KS other than those studies cited earlier.
- There are no studies showing effects of testosterone on pubertal development in KS over time (i.e., longitudinal).
- It is clear that the discussion of “critical developmental windows” as related to testosterone effects of the brain is highly relevant to KS outcome.
- These “windows” may coincide with the brain’s “readiness” to be exposed to sex steroid hormones that facilitate the development of optimal brain structure, connectivity and function.
- Therefore, new research on timing and duration of hormone intervention over time is critical for understanding pathways to better outcome.
And Don’t Forget Environmental Effects!

- All influences (leading to individual differences) other than genetic or hormonal factors
  - Parenting
  - Family Environment
  - Education
  - Peer group
  - Therapy
  - Socioeconomic status
  - Life events
  - Prenatal events
  - Illness
  - Nutrition

- No studies in KS on this topic either!
Building a More Complete Model of Brain and Behavioral Development in KS

- 47XXY
- Environment
- Prenatal Development
- Early Development
- Pubertal Development
- Adult Outcome

Hormonal Alterations
Precision Medicine Approach to KS: A New NICHD-funded Study at Stanford

■ There are huge gaps in our understanding of the neural effects of testosterone supplementation on adolescents with KS

■ The goal of the new project is to clarify the role of TRT on pubertal brain development and function and to test whether initiating this treatment in peri-pubertal males leads to improvements in executive and social-emotional functioning
  - What changes/improves, what does not change/improve
  - Does timing of TRT matter with respect to age or pubertal level make a difference
  - What cognitive-behavioral characteristics remain problematic after TRT – and how do we address these with additional interventions!

■ Overarching goal to generate research findings that will lead to new, disorder-specific treatment approaches and improved clinical outcomes
Study to Investigate the Effects of Testosterone on Brain and Behavior in KS

- Naturalistic (accelerated) longitudinal study of 60 boys with KS and 60 age-matched boys with typical development 9-13 years of age at baseline
- Will follow for up to 4 annual time points at either Stanford or Jefferson/Nemours (east coast families)
- Comprehensive cognitive-behavioral, social-emotional assessments
- Brain imaging (structure, connectivity, function)
- Hormone levels and assessment of puberty by pediatric endocrinology
- First-of-its-kind study will address important knowledge gaps

Please contact our study staff at
- 650-497-6525
- klinefelterssyndrome@stanford.edu

**Figure.** Schematic of hypothesized effects (100 in this example indicates average age-normed scores).
Particular thanks to......

■ Families who HAVE participated in our studies
■ Families who WILL participate in our studies in the future
■ National Institute of Child Health and Human Development
■ Vanessa Alshuler
■ Lara Foland-Ross
■ Judith Ross
■ Tandy Aye
■ David Hong
■ Research staff of the Center for Interdisciplinary Brain Sciences Center at Stanford