Brains, Genes, And Puberty: Testosterone Replacement Therapy in Klinefelter Syndrome

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Family Conference

Goals

Introduce Klinefelter Syndrome (KS)

Learn about differences in executive and psychosocial functioning as well as brain differences in KS

Discuss
how testosterone may play a role in the

KS phenotype

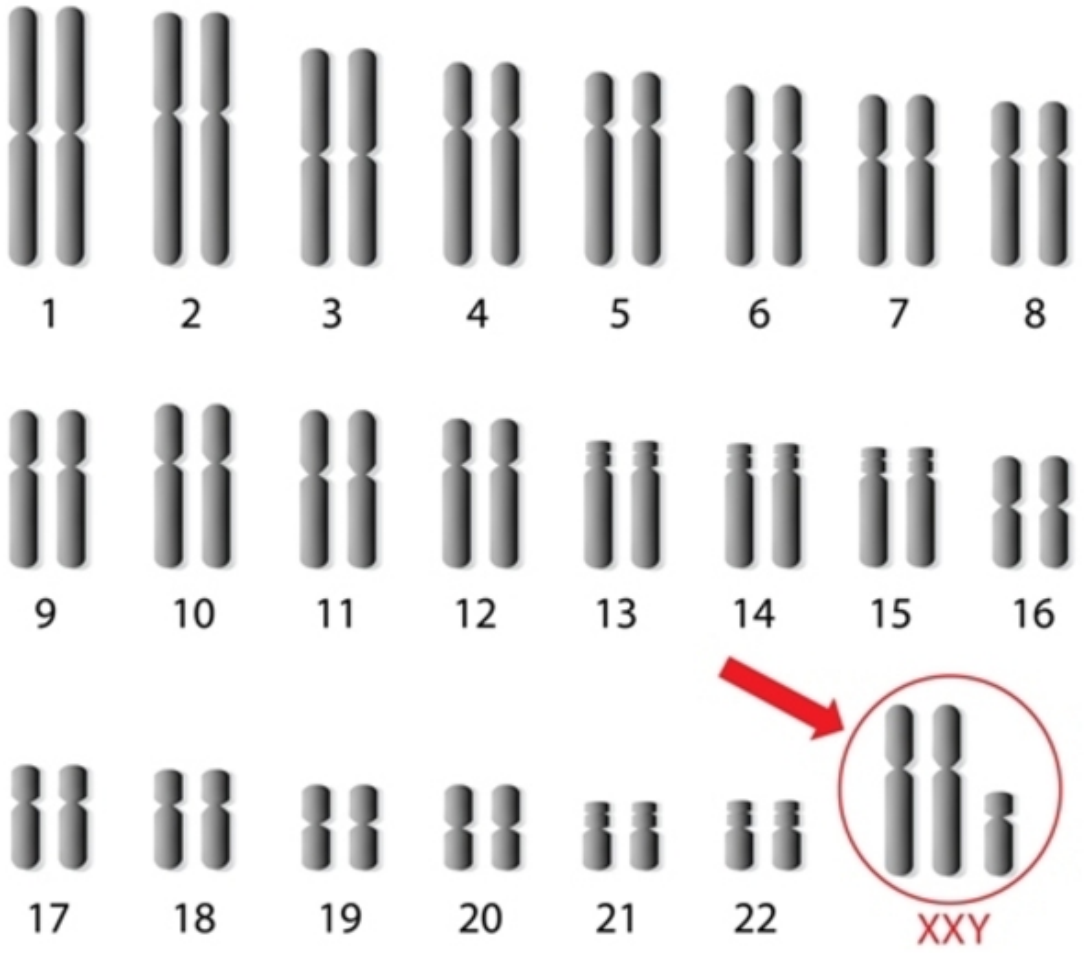
Explore the ways in which testosterone replacement therapy may affect brain and behavior

Describe current gaps in understanding and need for further research

Introduce a new research study at Stanford (BGAP Study)

Klinefelter Syndrome (KS)

- Genetic disorder that consists of a sex chromosome aneuploidy
  - Due to atypical number of X chromosomes
- Majority born with 47, XXY karyotype
- Most common sex chromosome condition

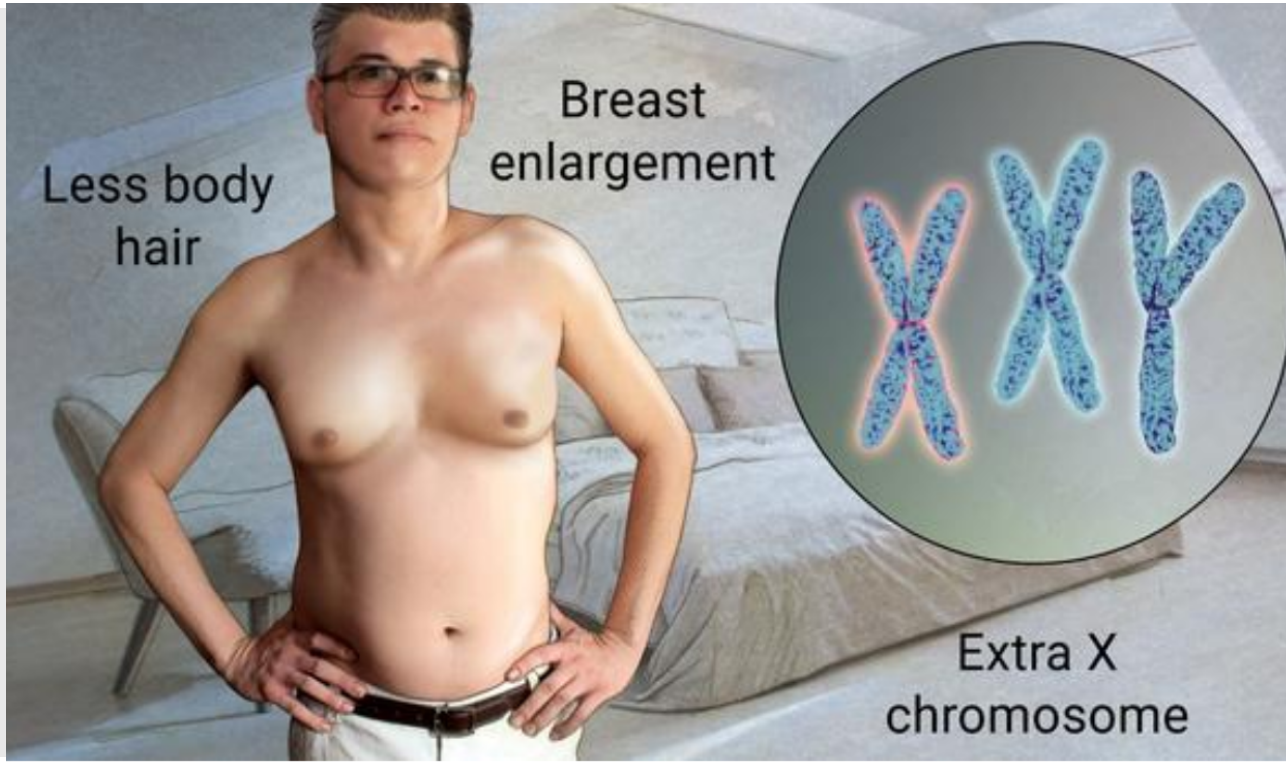


Credit: Alila Medical; Media/Shutterstock.com

Davis, et al., 2016

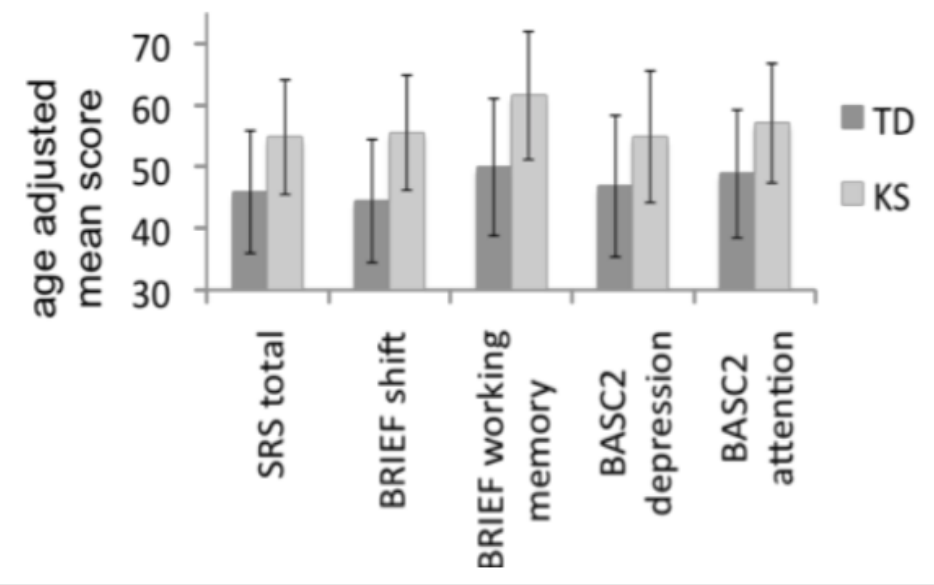
Common physical, behavioral, and neurocognitive traits

- Tall stature
- Testicular failure, reduced testosterone, impaired spermat ogenesis (creation of sperm)
- Gynecomastia (enlarged breast tissue)
- Delayed or incomplete puberty



Ross et al., 2008, 2017; Lee et al., 2011

Common physical, behavioral, and neurocognitive traits



- Increased behavior problems, social problems, and withdrawal (shyness, reduced self-esteem)
- Increased depression, anxiety, and social-emotional issues

Ross et al., 2008; 2017; Lee et al., 2011

Common physical, behavioral, and neurocognitive traits

- Motor dysfunction and impaired visual-motor integration
- Language based learning issues
- Deficits in executive functioning
  - Working memory
  - Sustained attention/inhibition

Ross et al., 2008; 2017; Lee et al., 2011

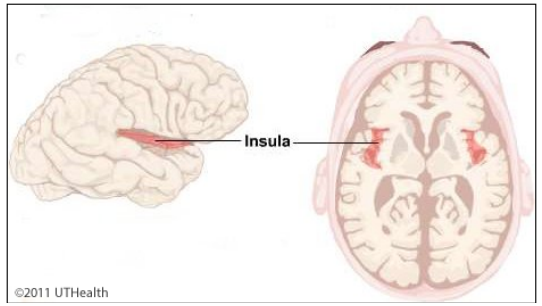
Impact of physical, behavioral, and neurocognitive traits

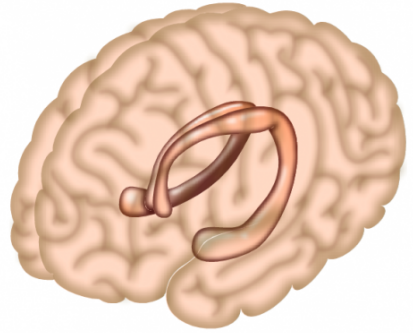
Samango-Sprouse et al., 2010; Lee et al., 2011

Brain differences in KS

Reduced volume in

- Hippocampus
  - Learning and memory
- Insular cortex
  - Interoception/emotion processing
  - Some aspects of executive function
  - Social cognition
- May be associated with verbal memory and mood disturbances

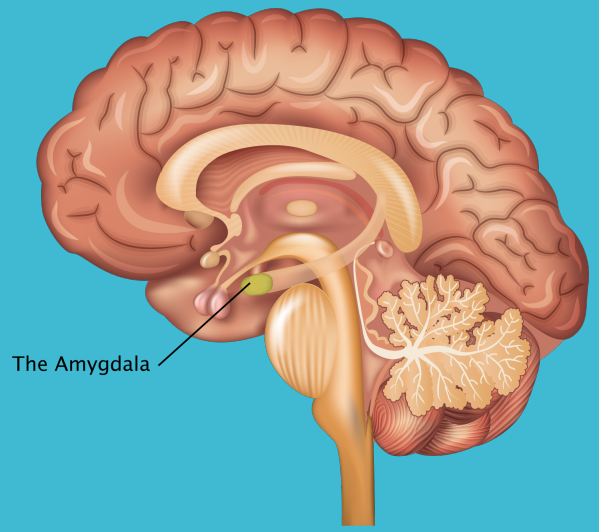




Hippocampus

Patwardhan et al., 2000, 2002; Bryant et al., 2011; Hong et al., 2014; Oh et al., 2014

Reduced volume in



Amygdala

Fear and anxiety	Processing of faces, emotions, and social stimuli

Social deficits and mood/behavior dysregulation

Patwardhan et al., 2000, 2002; Bryant et al., 2011; Hong et al., 2014; Oh et al., 2014

Reduced volume in

Temporal and frontal regions

Language and verbal memory

Decision making

Language and executive function/attention deficits

Patwardhan et al., 2000, 2002; Bryant et al., 2011; Hong et al., 2014; Oh et al., 2014

Increased volume in

Sensorimotor (precentral and postcentral gyri) and posterior-occipital regions (cuneus and precuneus)

Could explain the preservation of visuospatial abilities and/or may indicate compensatory neurodevelopment

Patwardhan et al., 2000, 2002; Bryant et al., 2011; Hong et al., 2014; Oh et al., 2014

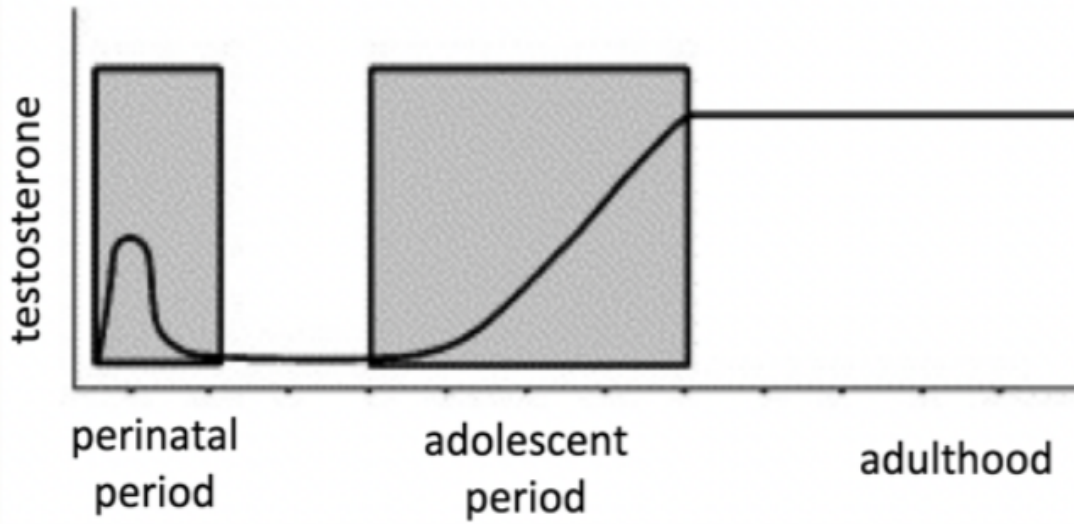
How can KS be treated?

Testosterone replacement therapy (TRT)

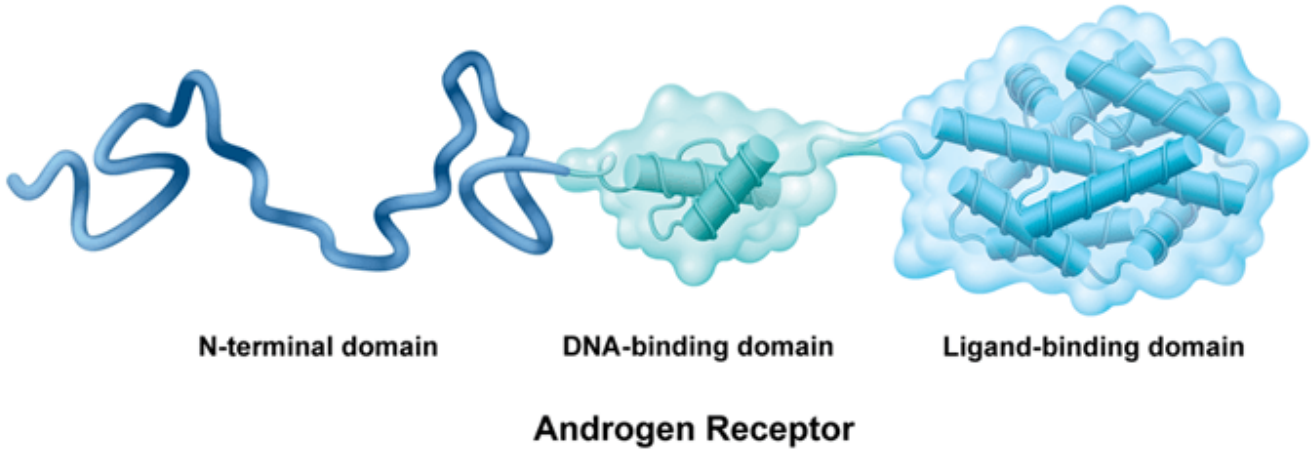
Puberty-associated neurodevelopment and the role of testosterone

- Two hormone-sensitive periods in brain development:
  - perinatal
  - peripubertal

- Adolescence is a developmental period where gonadal hormones (e.g. testosterone) organize brain and behavior



Testosterone changes through lifespan



- Several areas of the brain have androgen receptors
  - Hypothalamus
  - Amygdala
  - Hippocampus
  - cortex

- Recent research has found low testosterone levels as early as infancy or early adolescence in KS

http://www.essapharma.com/our-work/androgen-receptor/

Ross et al., 2005

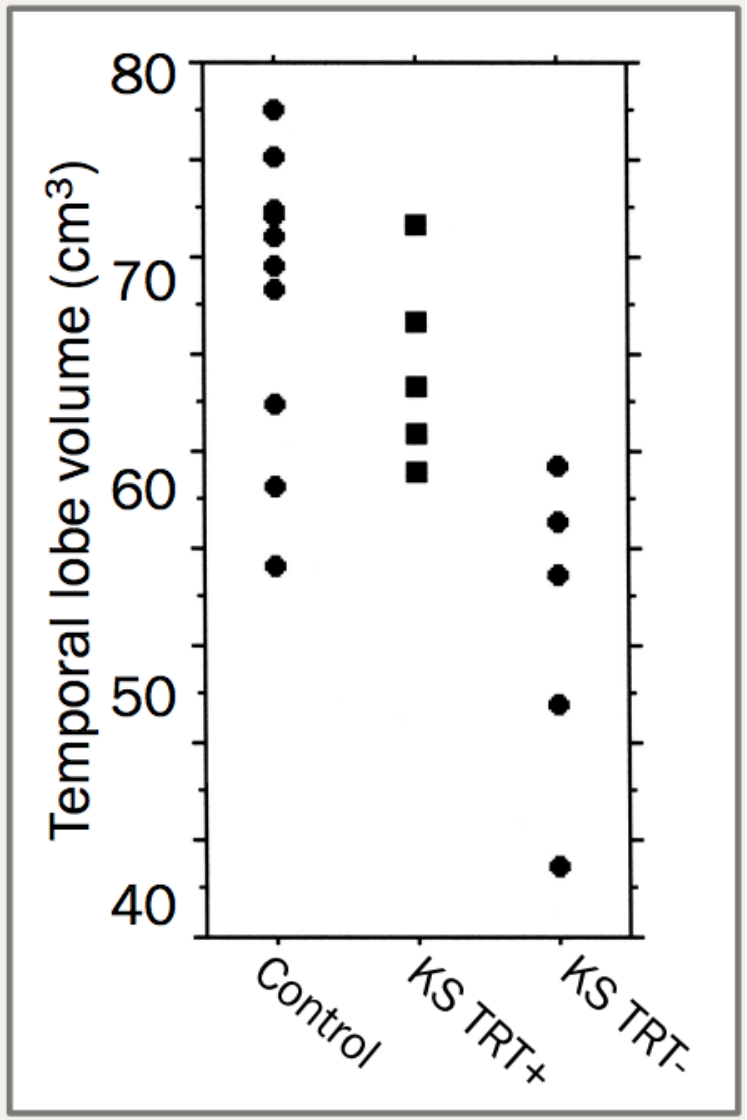
Influence of TRT on the brain and associated behavior?

TRT may increase temporal lobe size and improve verbal fluency in males with KS

- Retrospectively looked at testosterone effects in adults with KS
- 20 participants total (10 with KS 47, XXY; 5 with KS received TRT)

Patwardhan et al., 2000

- Temporal lobe volume was significantly larger in KS TRT+ compared to KS TRT-
- No significant difference in temporal lobe volume between KS TRT+ and TD group
- KS TRT+ had significantly higher verbal fluency scores than KS TRT-
- No difference is verbal memory scores between both KS groups



Patwardhan et al., 2000

KS boys treated with low doses of androgen (oxandrolone) showed improvement in visual-motor functioning, anxiety, and social functioning

- 2 year clinical trial
- Included boys ages 4-12 years of age
- Not the primary end point of the study but still important findings

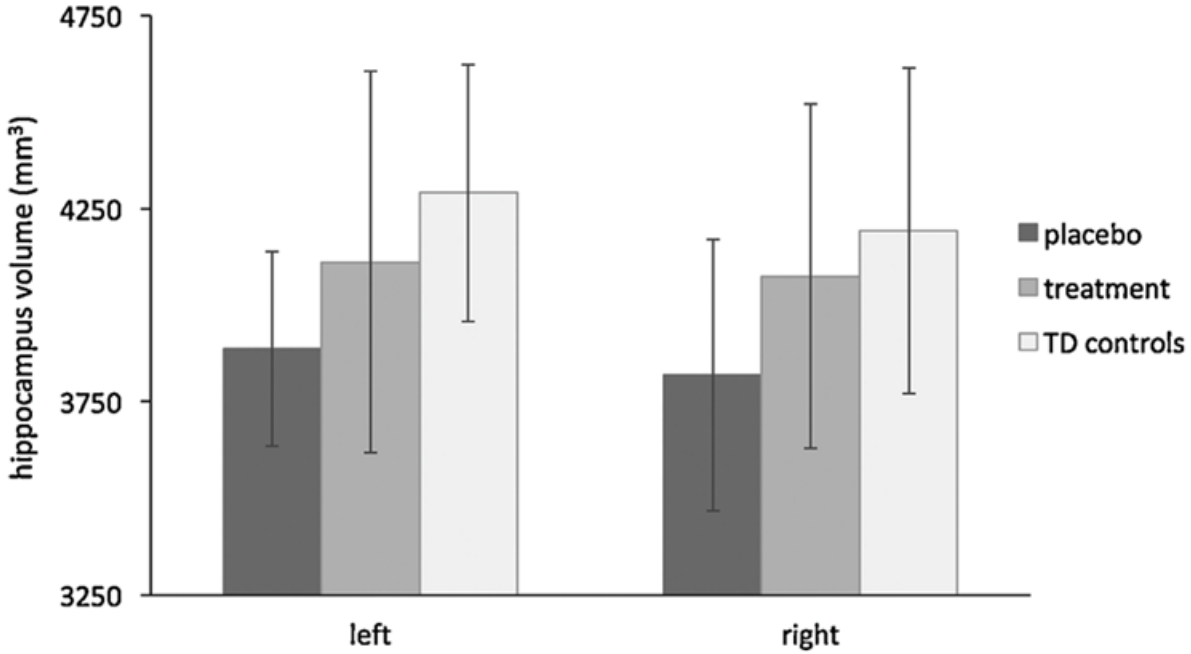
Ross, et al., 2017

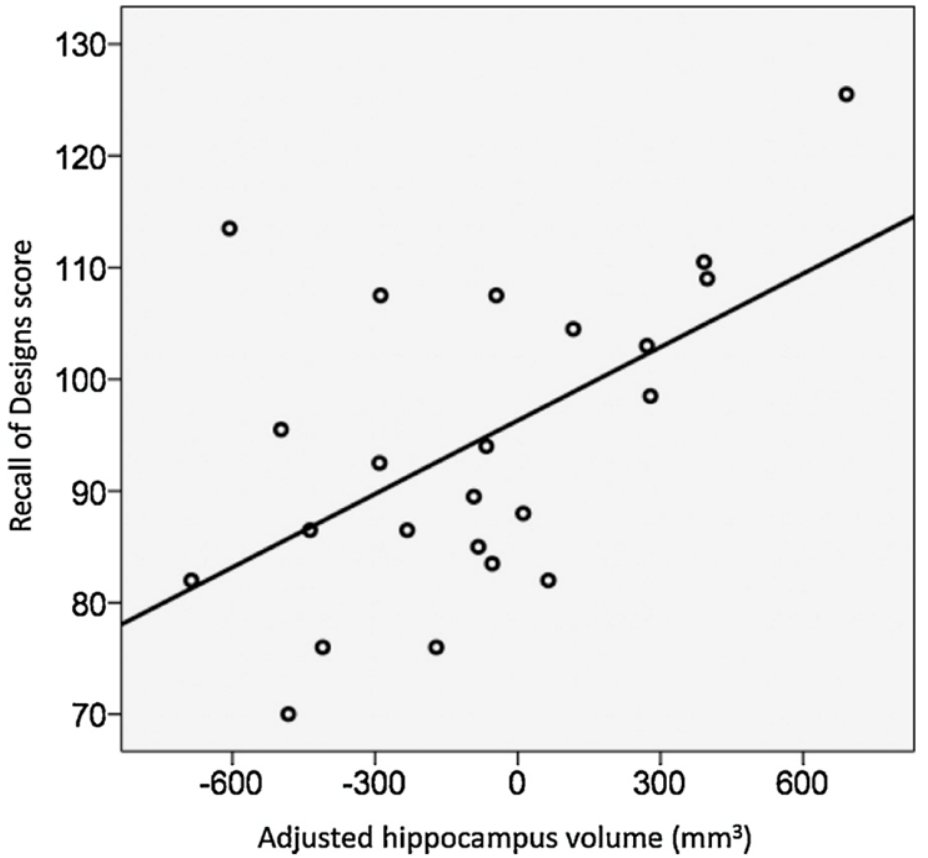
Low doses of oxandrolone might also cause increase in hippocampal size in boys with KS

- Subgroup of KS participants in oxandrolone clinical trial were scanned as well as TD controls

Foland-Ross, et al., 2018

Positive association between hippocampus volume and performance on spatial memory task





Larger hippocampal volumes with treatment in KS

Foland-Ross, et al., 2018

Testosterone treatment is associated with reduction in depressive symptoms

- Study broadly looking at the effects of testosterone in men without KS
- Adult participants, varied ages, hypogonadal and eugonadal

Walther et al., 2018

Early hormone therapy (EHT) during infancy in KS

- Positive treatment effects in the following domains:
  - Speech and language development
  - Reading skills
  - Verbal and non-verbal intellectual quotients
  - Neuromotor planning and execution
- Fewer behavioral problems:
  - Externalizing behavior problems
  - Aggressive behaviors
  - Schooling behavior
  - Affective problems

Samango-Sprouse et al., 2013, 2015

Current gaps in understanding

Very little data available about the effect of hormone intervention in KS other than those studies discussed earlier

No studies have yet systematically assessed the influence of TRT on brain function or associated cognition in adolescent boys with KS

No disorder-specific treatments (other than TRT) for brain dysfunction in KS

BGAP STUDY

BRAINS, GENES, AND PUBERTY

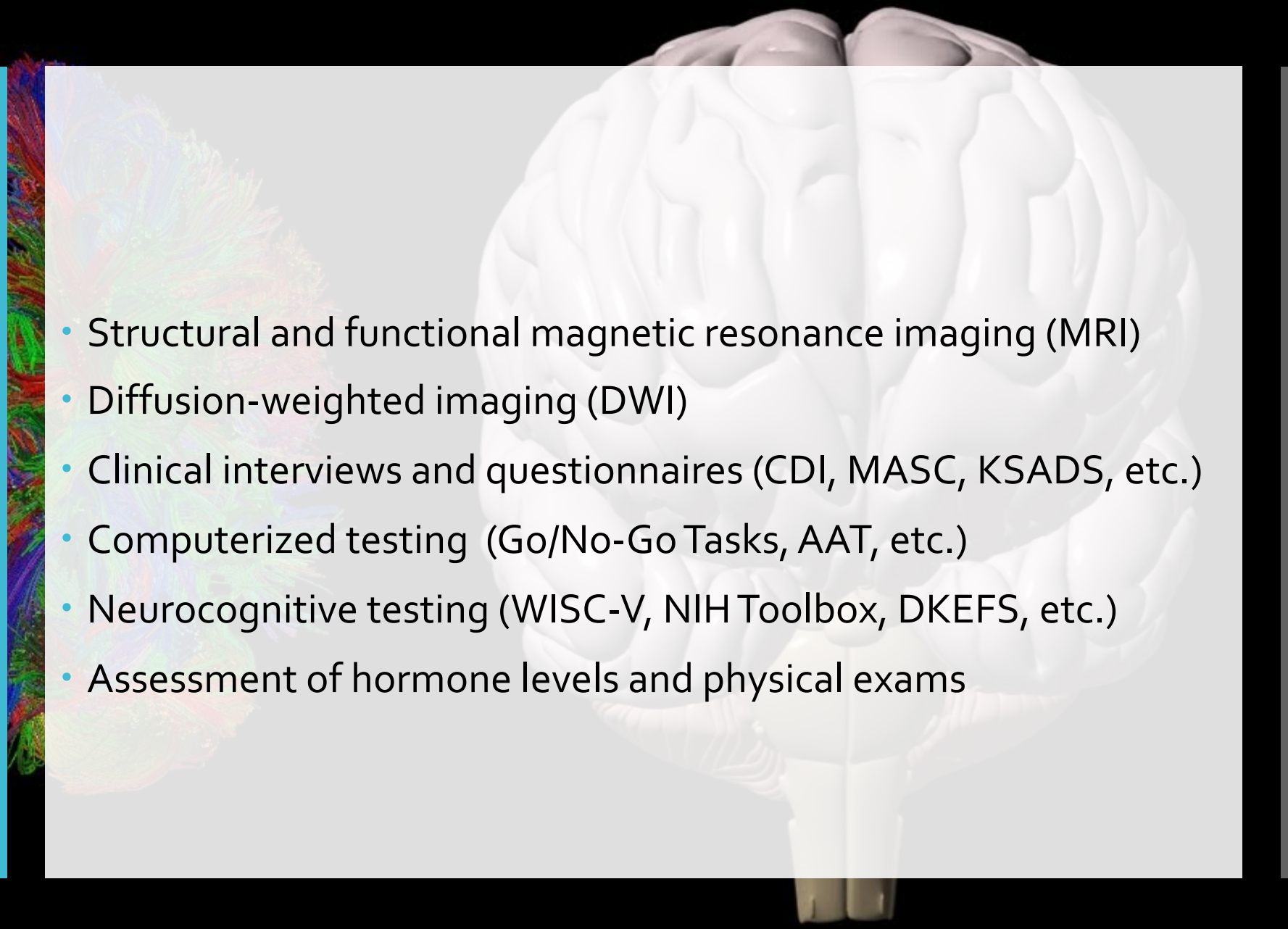
New NICHD-funded Study at Stanford and Nemours (Reiss & Ross)

- 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

So what's wrong with current approaches to cognitive and behavioral challenges in KS?

- Actually, nothing
- Always use the best treatment modalities you have available at present (preferably evidence-based!)
- But current symptom-based treatments are always going to be limited in effectiveness because they were not developed for KS!
- Persistent problems with cognition (particularly executive function) can have long-term, significant effects on outcome
  - Vergunst et al.: Association between childhood behaviors and adult employment earnings in Canada JAMA Psychiatry, 2019

Methods

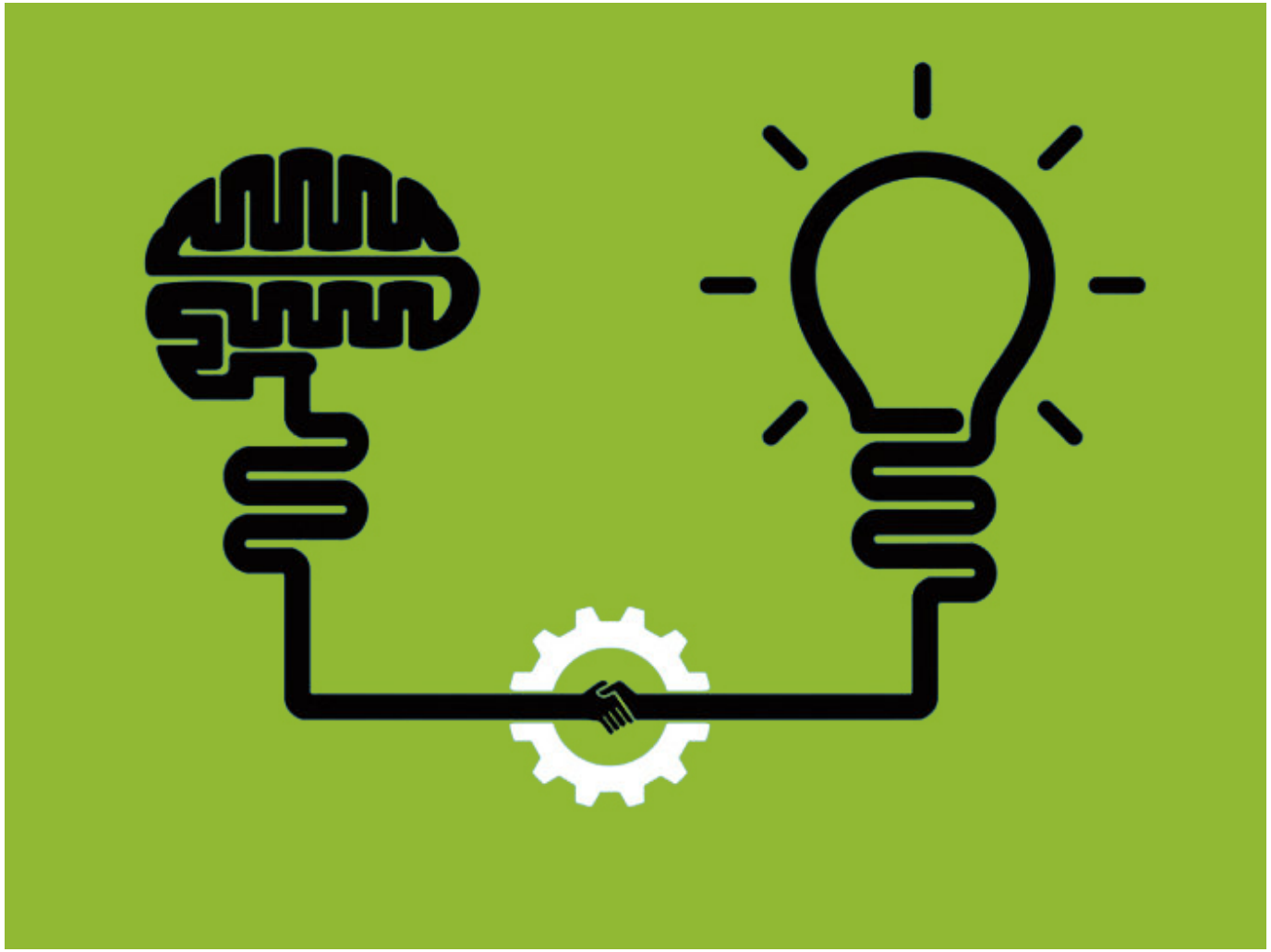


- Structural and functional magnetic resonance imaging (MRI)
- Diffusion-weighted imaging (DWI)
- Clinical interviews and questionnaires (CDI, MASC, KSADS, etc.)
- Computerized testing (Go/No-Go Tasks, AAT, etc.)
- Neurocognitive testing (WISC-V, NIH Toolbox, DKEFS, etc.)
- Assessment of hormone levels and physical exams

Accelerated Longitudinal Design

Naturalistic study design

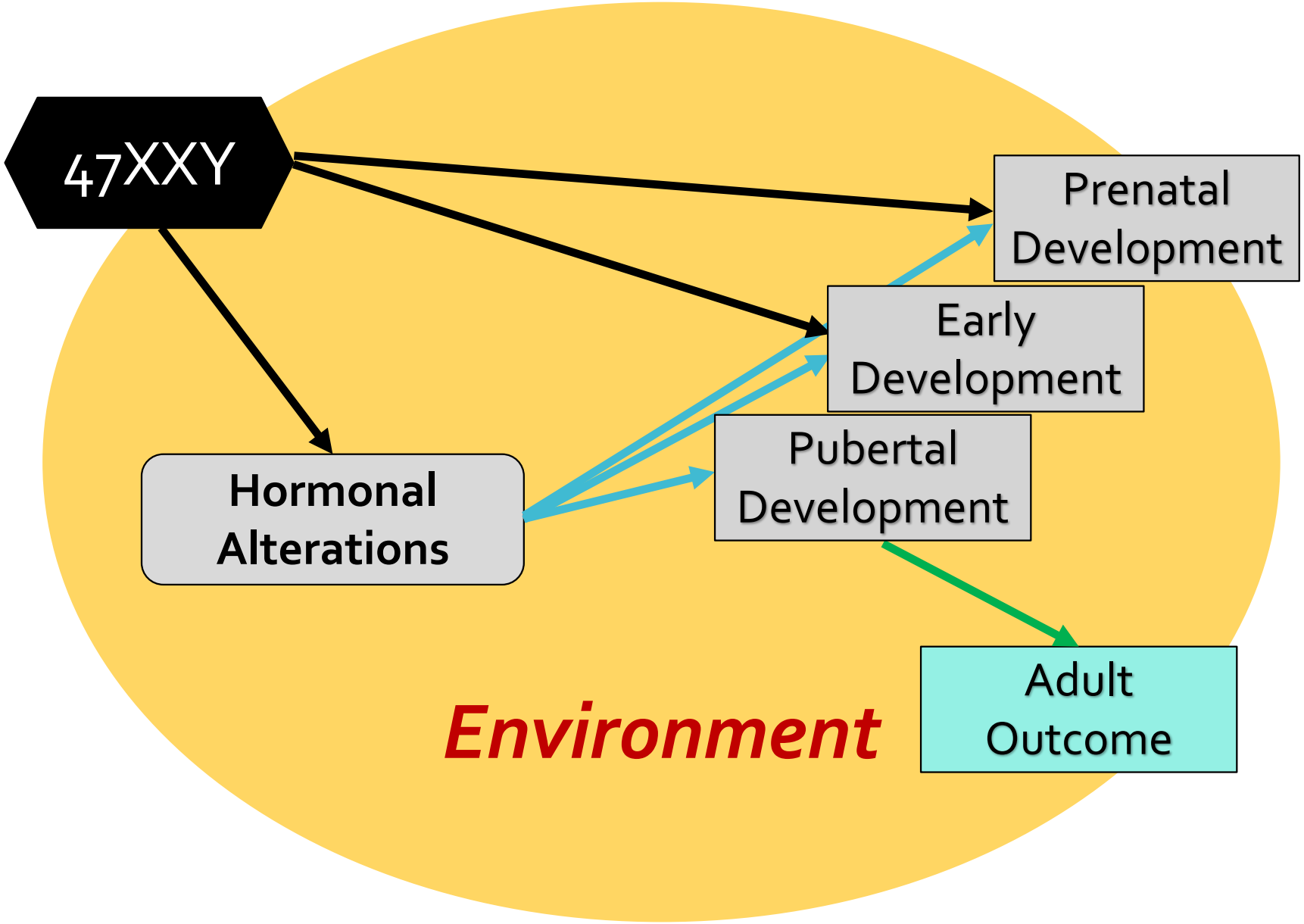
Primary goal is to clarify brain and behavioral changes in KS associated with TRT as it is administered in typical clinical practice



Innovation

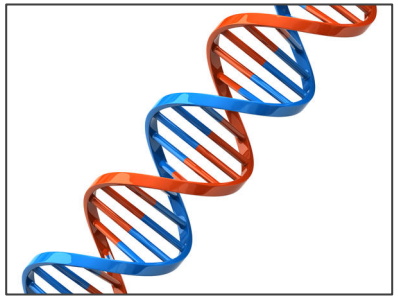
- First-of-a-kind study
- Longitudinal design including up to 4 time points
- Multi-level approach (behavior, cognition, TRT, brain, environment)
- Impacts outside of KS
- Findings will help inform the development of more effective, disorder-specific treatments for KS

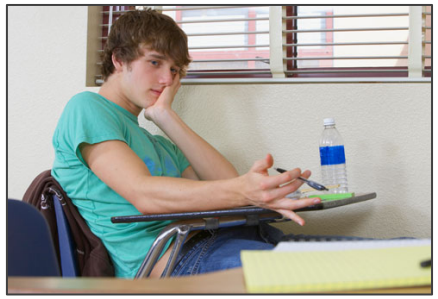
Building a more complete model of brain & behavioral development in KS



Building a precision medicine approach to KS

	Yesterday	Today	Tomorrow
Data	Symptom-Based	Cohort-Based	*Algorithm-Based*
Actions	Intuition Medicine	Evidence-based Medicine	*Precision Medicine*





- Brain development & function
- Genetic & molecular profile
- Physiological profile
- Treatment response
- Family environment
- Cognition and behavior

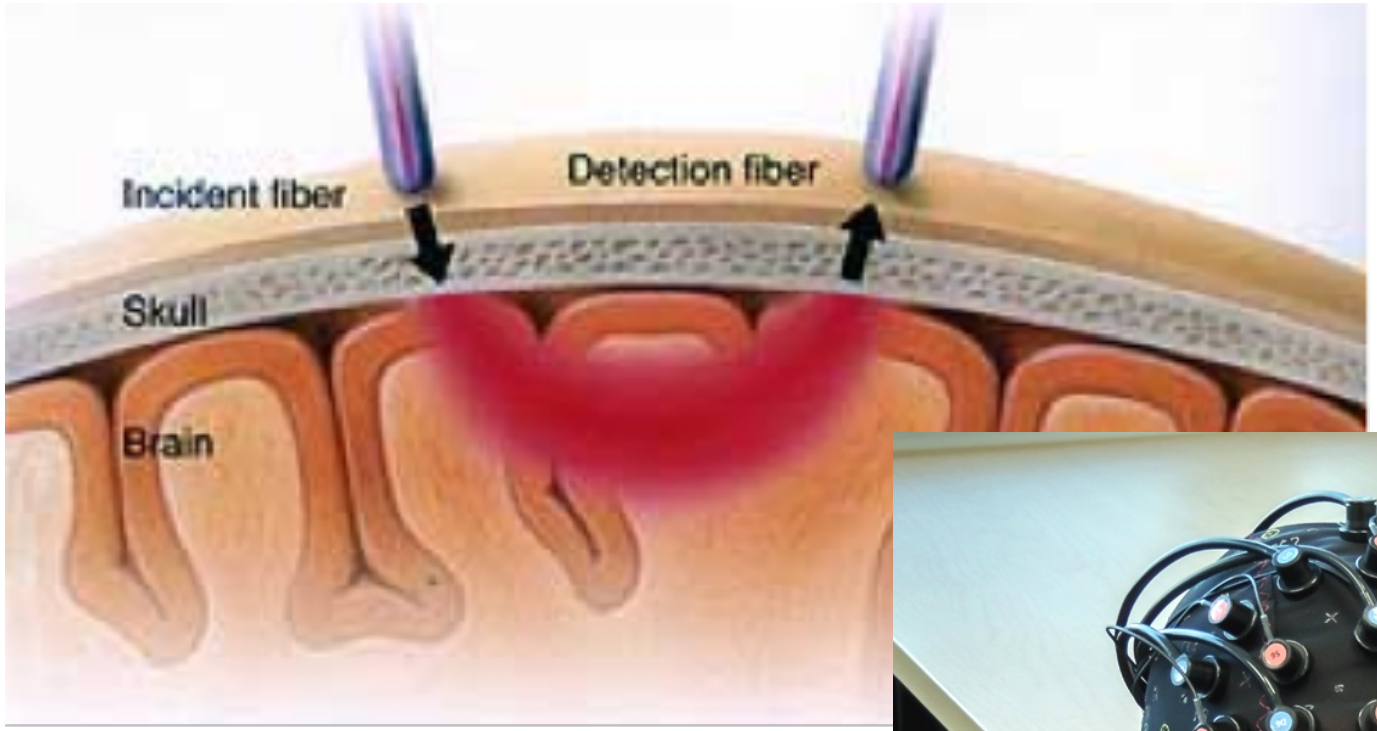
Big data analytics (TDA, ML)
Reference databases/algorithms

Precision Medicine for KS

Some initial ideas for a precision medicine approach to KS

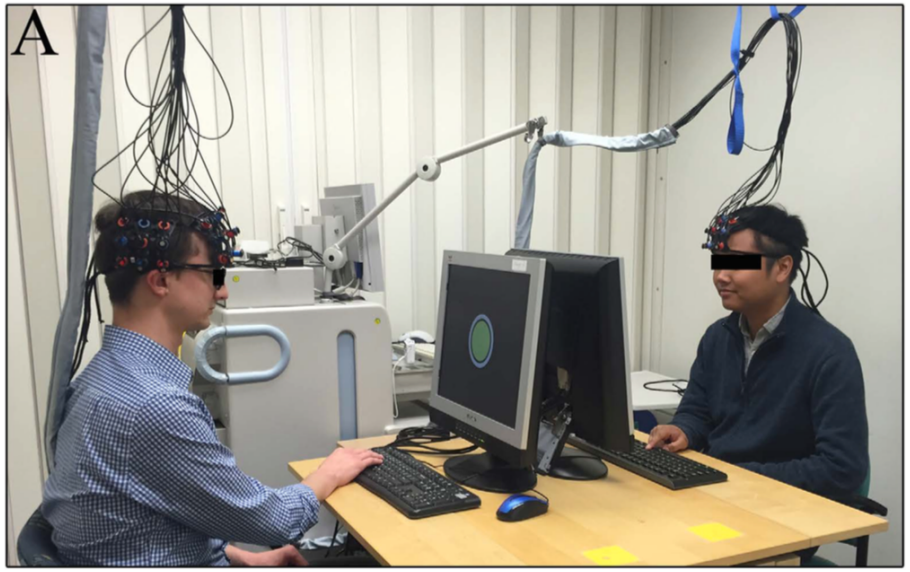
- Optimize TRT treatment in light of a better understanding of brain, cognitive-behavioral and social-emotional development in KS
  - Assess dose, duration and timing (developmental windows)
  - Consider possibility of KS "subgroups" in terms of response
- Develop new cognitive-behavioral and social-emotional treatments that take advantage of, and target the specific profile or strengths and weaknesses in KS
  - Computer-based cognitive training to enhance specific executive functions
- Develop innovative, imaging-based interventions that have the potential to amplify hormone and cognitive-behavioral/social-emotional treatments to enhance outcome
  - fNIRS-based real-time feedback to enhance executive function
  - Hyperscanning to enhance social-emotional function

Functional Near-Infrared Spectroscopy (fNIRS): A method for obtaining functional brain imaging data in naturalistic settings

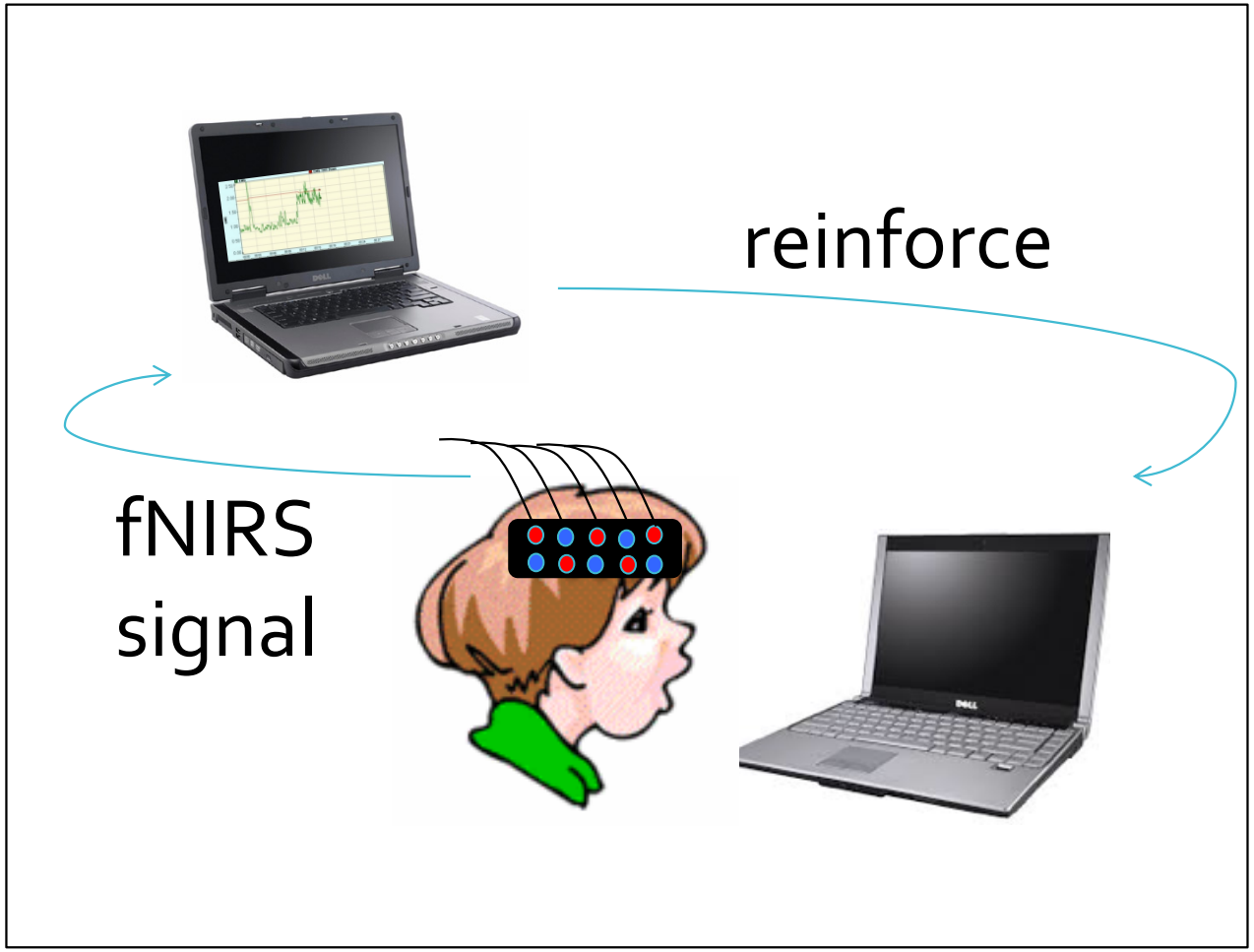


Potential Therapeutic Applications of fNIRS in KS

Hyperscanning



Neuro-feedback



Hyperscanning + Neuro-feedback!

To learn more about the study, visit our website at:

- med.stanford.edu/BGAPstudy

Interested in being a part of our study? See if your son is eligible by visiting:

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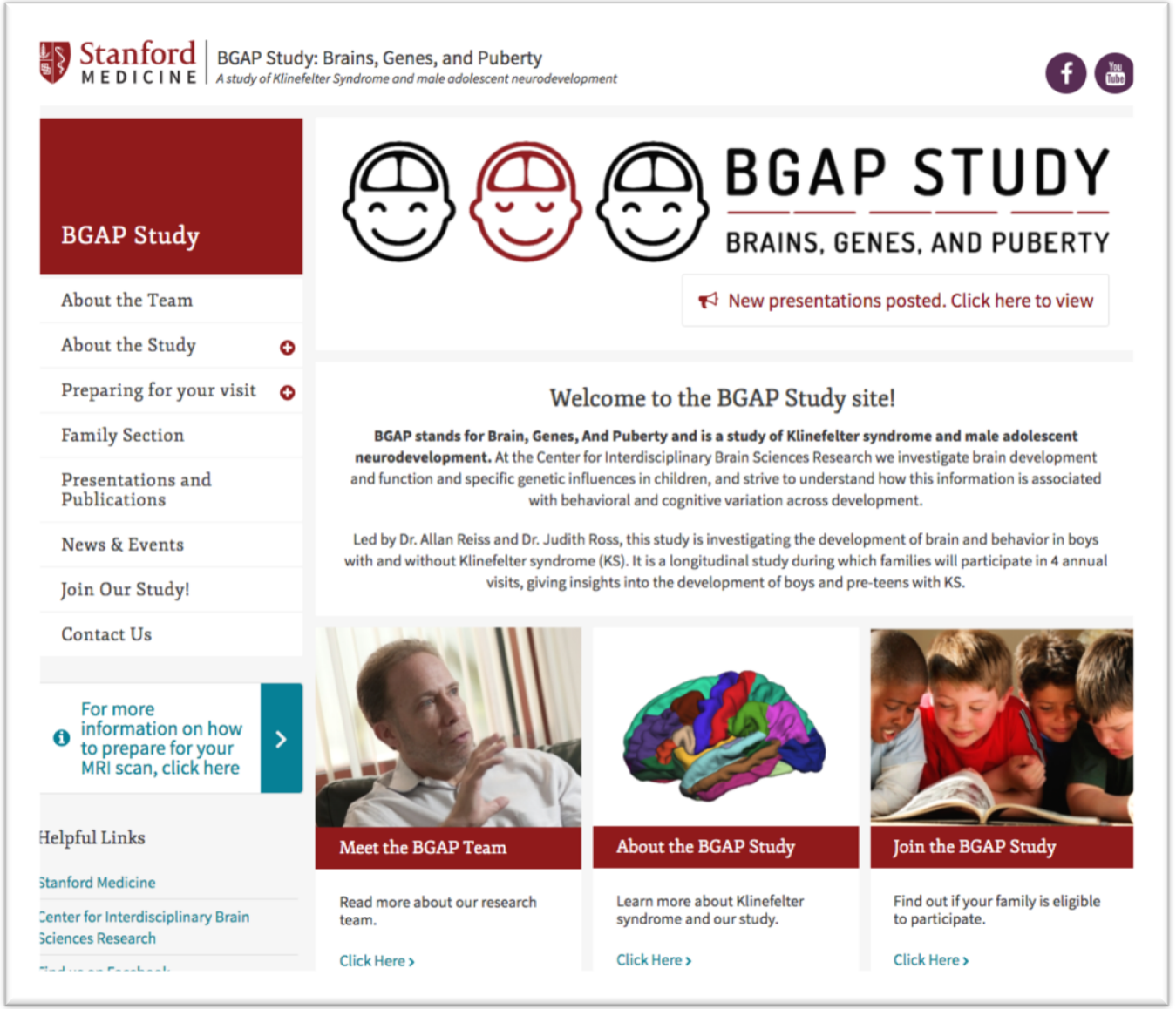

Thank you

And questions