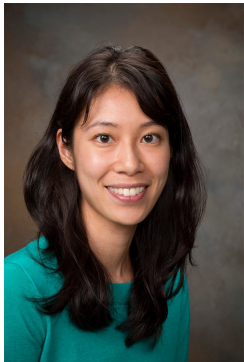


# Advancing Pediatric Mental Health Research



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*Access Mental Health, Clinical Conversations*

January 5, 2023



# Outline

- Overview of Pediatric Clinical Research
- Pediatric Depression Research
- Pediatric Irritability Research
- Pediatric Emotional Regulation Research

# What is Pediatric Clinical Research?

*A systematic investigation into the medical conditions and treatments relevant to those who are under 18 years of age.*

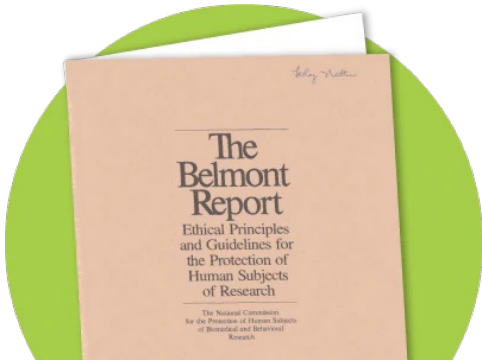


# Why is Pediatric Clinical Research Necessary?

- Most products are not approved for children because of limited research into their efficacy and safety in children. This is especially true in mental health research!
- Children are not small adults (Denne and Hay, JAMA Pediatrics 2013). Data from adult studies cannot be extrapolated to children.
- Developmental stages are heterogenous, and specific research may be needed for specific pediatric groups (ex: neonates vs. toddlers vs. school-age children vs. adolescents)

# A Brief History of the Inclusion of Children in Medical Research

- Between 1975-1976, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research examined autonomy in the ethics of pediatric research.
- This examination was motivated by multiple reports from the 60's and 70's about dangerous and coercive research practices in children, particularly those in institutionalized settings, such as orphanages.
- This also coincided with the work that eventually became the Belmont Report



Carroll and Gutmann, 2011



# A Brief History of the Inclusion of Children in Medical Research

- At the heart of some of the deliberations was what it meant to provide consent.
  - If voluntary consent was absolutely essential, children and those unable to provide consent may be excluded from research.
  - Some argued that the exclusion of children would stagnate medical progress, that pediatric physiology was inherently different from adult physiology
  - Others additionally argued that society had a moral duty to alleviate childhood illnesses and also study the roots of adult-onset illnesses, and this necessitated research with children, even if that research was not directly beneficial to the child participants of medical experiments.

Carroll and Gutmann, 2011

# A Brief History of the Inclusion of Children in Medical Research

- The commission concluded that involving children in research was of particular ethical concern due to children's reduced autonomy and inability to give fully informed consent.
- Yet, research on children was viewed as critical for developing 'new treatments or preventative methods for conditions that jeopardize the health of children'.
- As part of this, all research activities were required to be reviewed by the IRB, and at Yale, a special pediatric review board
- Parents would provide consent, and children seven or older would provide assent.



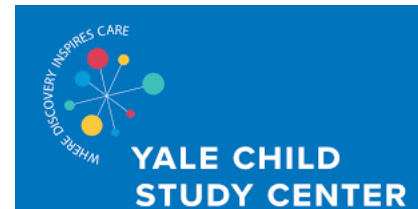
Carroll and Gutmann, 2011

# The Inclusion of Children in Medical Research Today

- Today, those < 18 y/o have been deemed a critical and vulnerable population for research studies. Projects supported by the NIH and the FDA must justify why pediatric populations are *not* included, if the illness is one that occurs in both children and adults.
- The Pediatric Research Equity Act was passed in 2003, which required that all new drugs submitted to the FDA assess the safety, effectiveness and dosing in pediatric subpopulations (prior to this drug companies were allowed to either label medicines with disclaimers that they had not been tested in children, or extrapolate to children based on adult data).



Carroll and Gutmann, 2011  
Denne and Hay, 2013  
Hill et al., 2014





# What are the Barriers to Pediatric Clinical Research?

- Recruitment for studies is difficult
  - <31% of pediatric trials in Britain met recruitment targets between 1994-2002 (McDonald, Trials)
  - ~46% of pediatric trials experience delays in the recruitment timeline (Denhoff, 2015) (about 50% achieved 80% or more of the enrollment goal)
- Families may not understand what research is and what it is designed for
- It can be difficult to find information about available studies

<https://www.socra.org/blog/pediatric-recruitment-what-works-and-what-does-not-work/>

# And Yet....



Advances from research can have enormous repercussions, such as

- Improved survival rates in pediatric cancers
- Decreased transmission of HIV from pregnant mothers to infants
- Improved survival of premature babies with the use of surfactant
- Eradication of polio
- Decreased morbidity and mortality in COVID-19

# Advancing Pediatric Mental Health Research

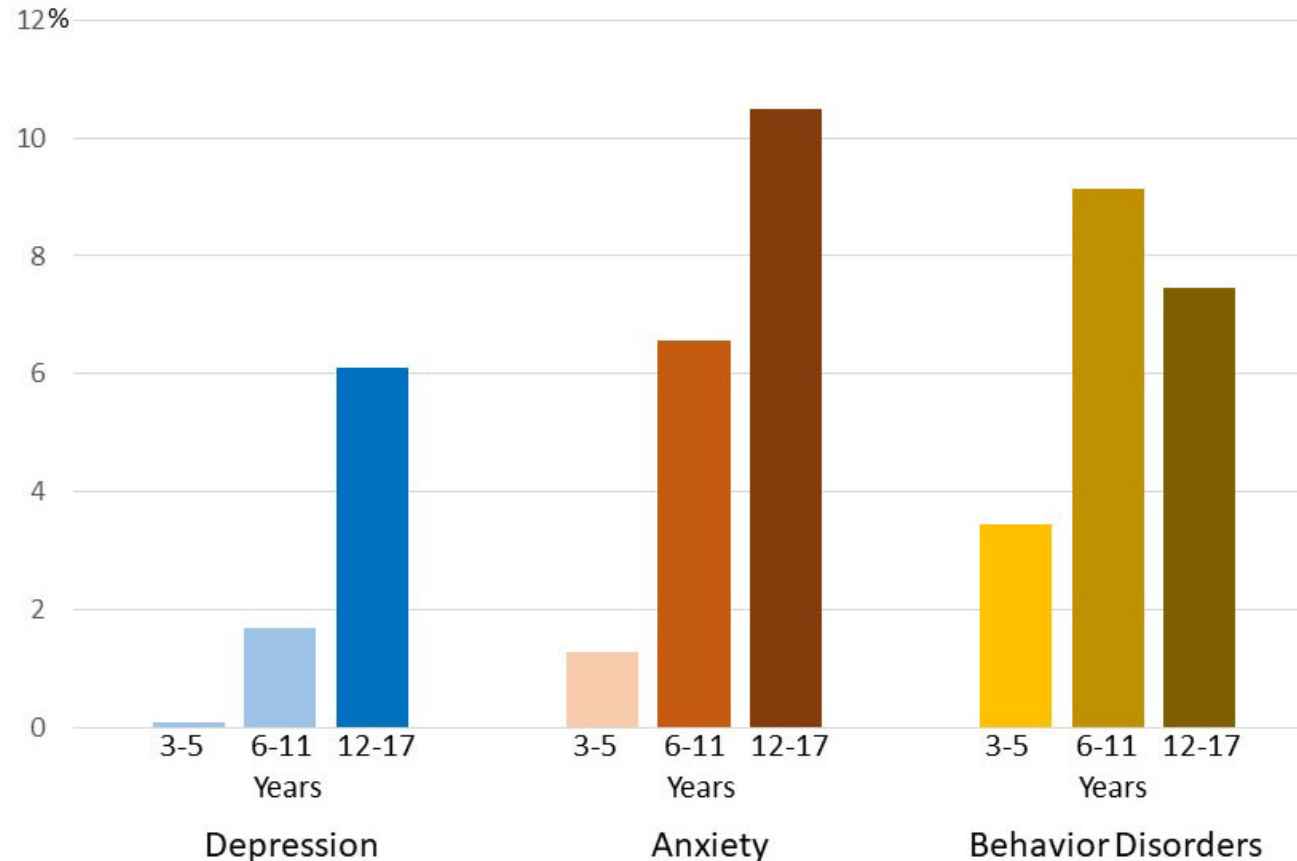


- Pediatric mental health disorders continue to be common and burdensome
  - 1 in 5 children between 3-17 y/o has one or more mental health disorders (CDC, 2019)
  - Mental health disorders are commonly comorbid (ex: 75% of teens with depression also have anxiety)
  - 1 in 5 teens has seriously considered suicide in the prior year (from 2019)
- \*\*To compare with other common pediatric illnesses:
- asthma is 1 in 12 (<18 y/o)
  - obesity is 1 in 5 (<18 y/o)

# Advancing Pediatric Mental Health Research



Depression, Anxiety, Behavior Disorders, by Age



<https://www.cdc.gov/childrensmentalhealth/data.html>

# Advancing Pediatric Mental Health Research—types of studies



- Treatment trials
- Mechanistic studies
  - What are the neurobiological, social, familial, environmental and individual characteristics that contribute to developing mental illnesses in childhood and adolescence?

# Where to Find Pediatric Mental Health Research



- Yale Center for Clinical Investigation (YCCI): [yaletrials.org](http://yaletrials.org)
- [ClinicalTrials.gov](http://ClinicalTrials.gov)
- Yale Child Study Center website:  
<https://medicine.yale.edu/childstudy/research/>
- Flyers from today's speakers:  
<https://drive.google.com/file/d/1sOGpEIFRIY0EtWaEh2XV5ocmSASzJTiw/view?usp=sharing>

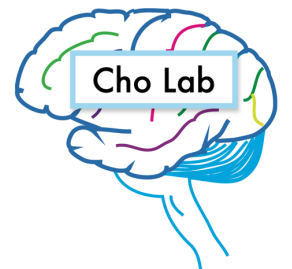
**\*\*\*Many of these studies also recruit typically developing children and teenagers\*\***

# Motivation and Cognition in Adolescent Depression

**Youngsun T. Cho, MD, PhD**

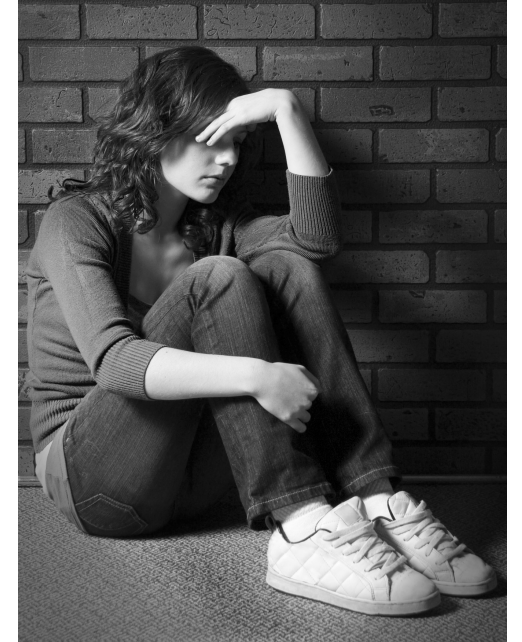
Assistant Professor, Yale Child Study Center and Department of Psychiatry  
Principal Investigator of the Cho Lab

**Jan 5, 2023**



# Adolescent Depression is a significant public health problem

- Nearly 1 in 5 will experience major depressive disorder (MDD) during the adolescent years (since COVID, may be closer to 1 in 4)
- Suicide is the 2<sup>nd</sup> leading cause of death in this age group
- Teen depression is associated with increased risk of poor social and academic functioning, early pregnancy, physical illness, and substance abuse
- Depression that begins in adolescence is associated with persistence into adulthood, with more severe clinical courses compared to later-onset MDD
- 70% of teens with depression experience recurrent depression within 5 years



*Promptly identifying and treating teenage depression is important*



# Risk factors for Adolescent Depression

- Family history of depression or other mood disorders
- Female—depression occurs 2-3x more often than in males
- History of early-life stress or adversity
- Poverty
- History of, or current, trauma
- Peer conflicts (ex: bullying)
- Familial conflicts or stress
- Minority stress
- Disability

## ***Per the CDC, in 2021, since the pandemic started:***

- 55% of high schoolers have reported emotional abuse from an adult in the home
- 11% have experienced physical abuse from an adult in the home
- 29% have had a parent or adult in the home lose a job.

# How does depression present in teenagers?

Persistent low mood or sadness OR irritability for at least 2 weeks

*PLUS* at least 4 of (**SIG E CAPS**):

- **S**leep Changes (either increased or decreased) (**S**)
- Loss of **i**nterest or motivation (**I**)
- **G**uilty feelings (**G**)
- Decreased **e**nergy (**E**)
- **C**ognitive difficulties—concentration, memory, etc (**C**)
- **A**ppetite Changes (either increased or decreased) (**A**)
- **P**sychemotor agitation or slowing (moving faster or slower) (**P**)
- **S**uicidal thoughts and behaviors (**S**)

*Depression can be marked by different symptoms for different teens*

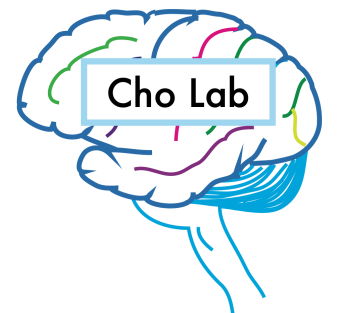


# Examining Motivational Effects on Cognition Adolescents with Depression

- **Cognitive impairment** is a prominent symptom of depression in teens
  - Poorer functioning (school and home obligations)
  - Worse emotional regulation
- **Motivational deficits** are common in teens with depression
  - Impaired decision making
  - low positive affect in children related to later depression

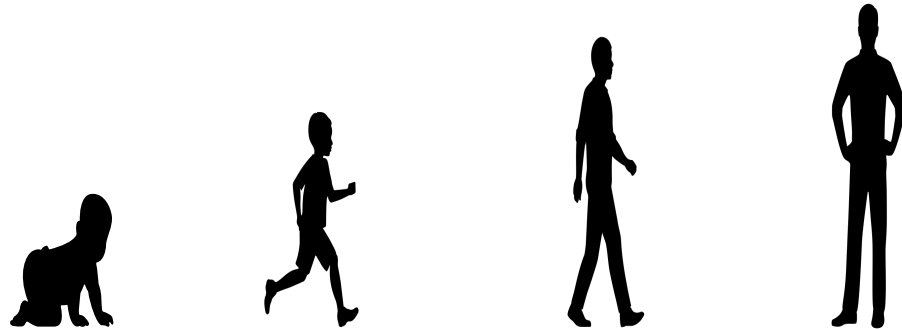
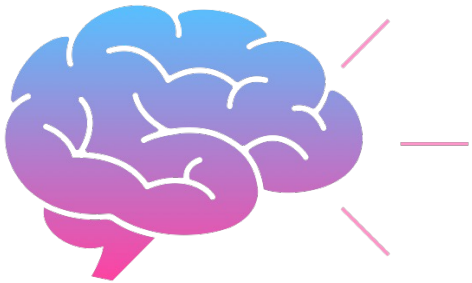
*What neural disruptions are associated with cognitive impairment and motivational deficits in adolescents with depression?*

*Over time?*



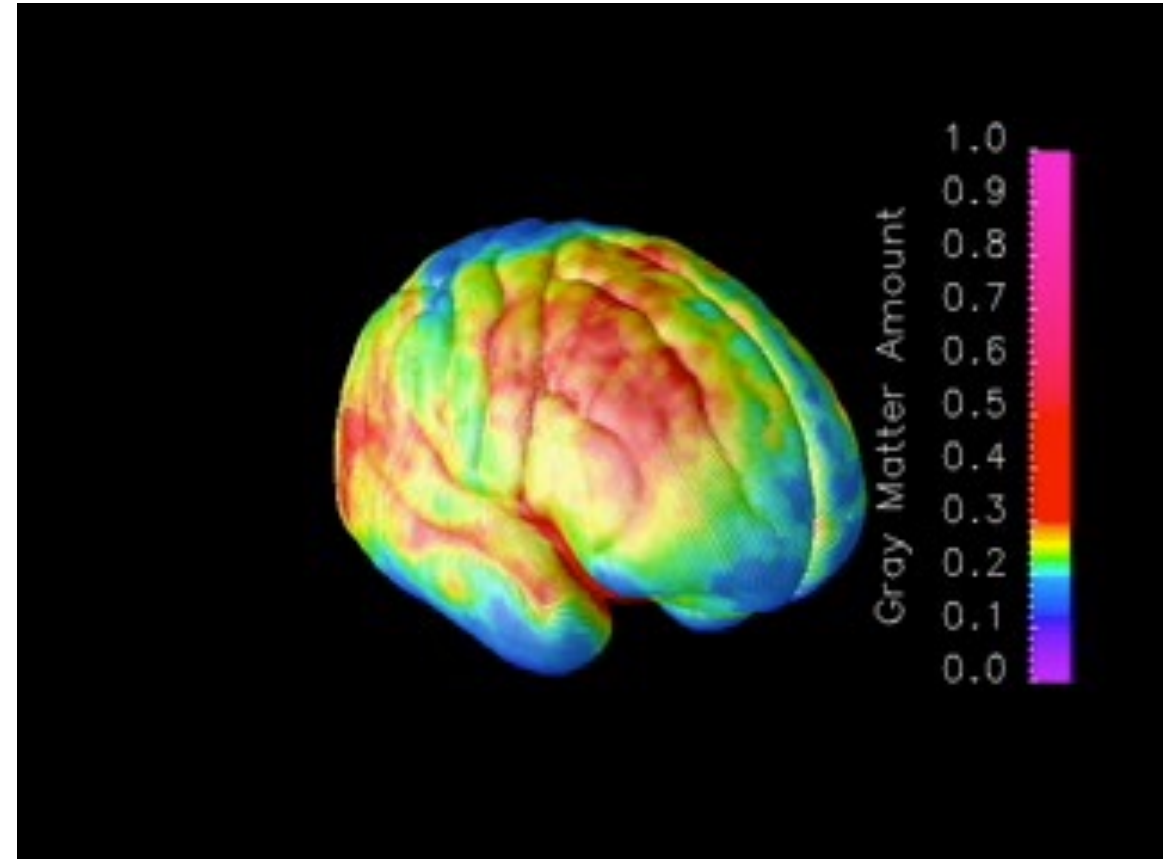
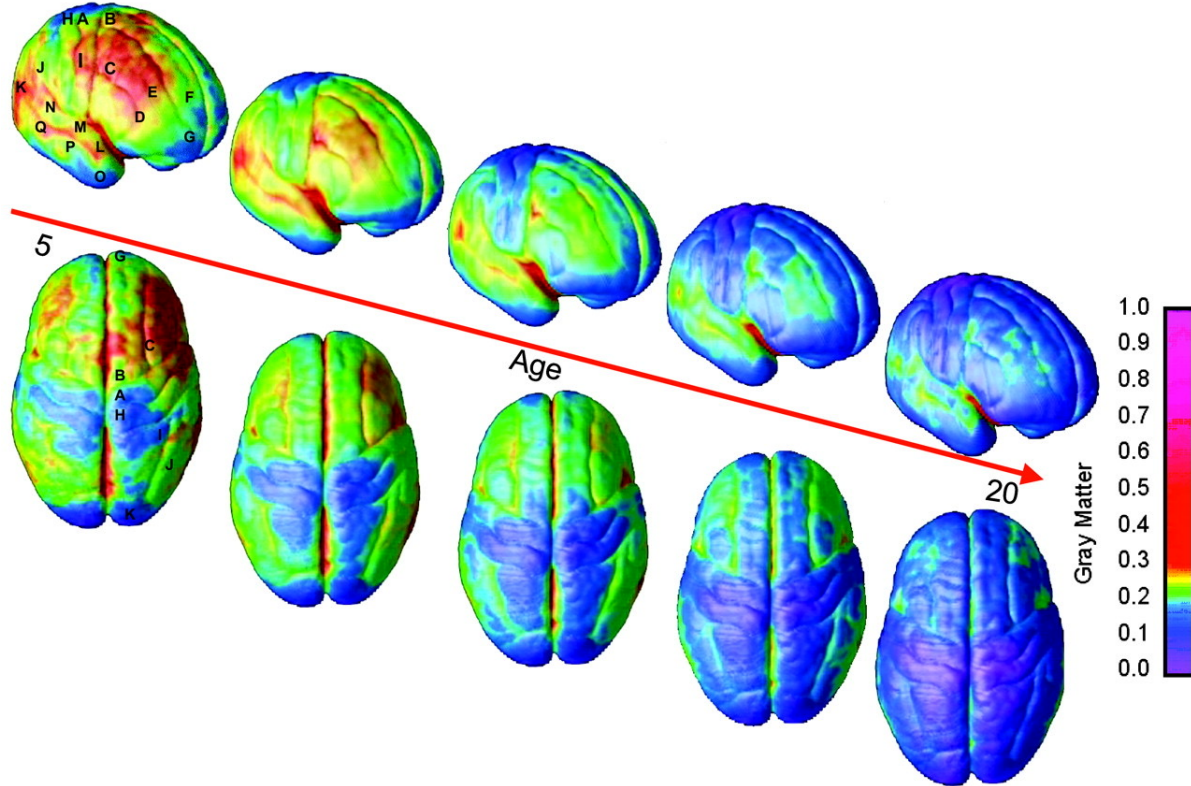
# What is special about the adolescent years?

- Rapid physical, emotional, social and cognitive growth
- Developmental changes in the brain parallel this growth and continue into young adulthood
- This growth allows teenagers to explore their identity
- Ideally, this developmental stage leads to successful transition to adulthood.



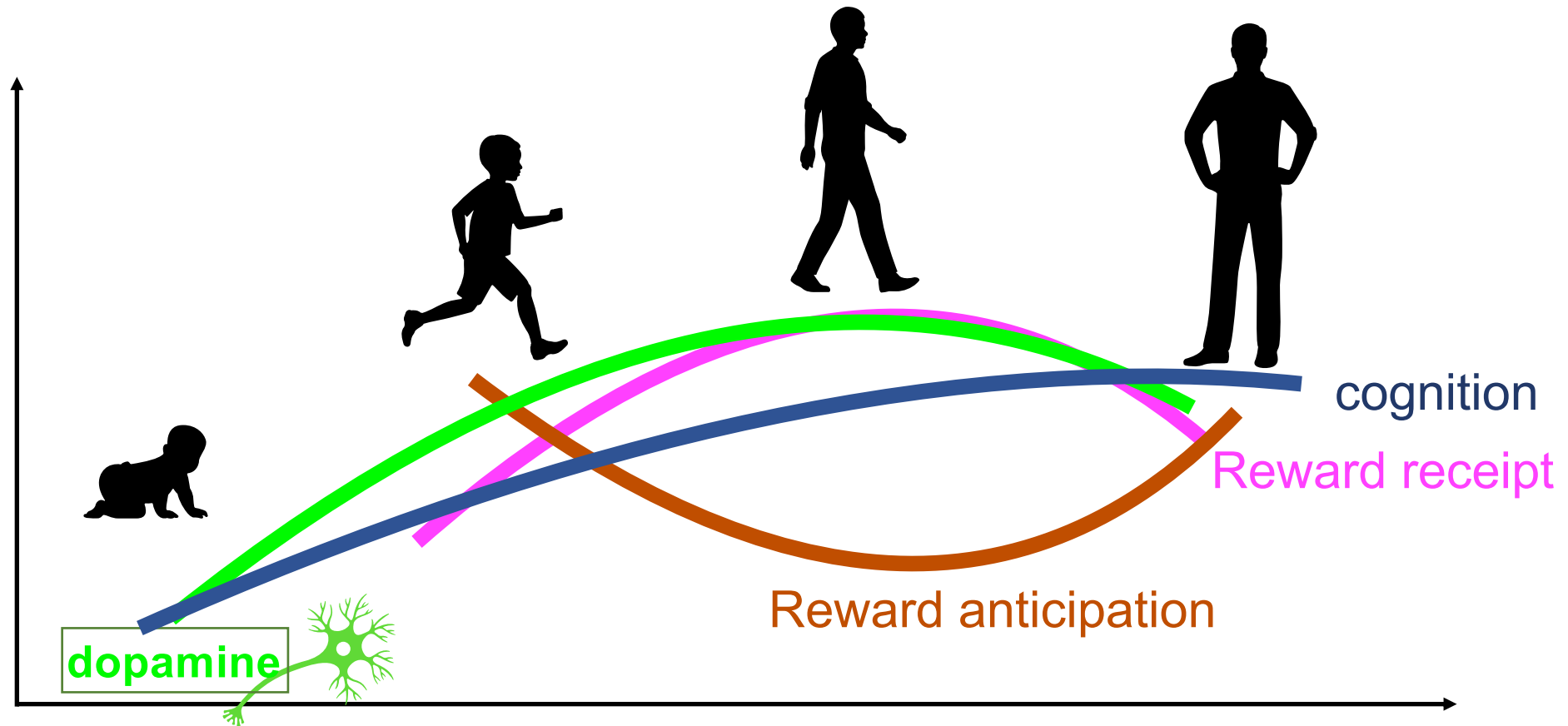
# Brain Changes During Adolescence

Gogtay et al 2004

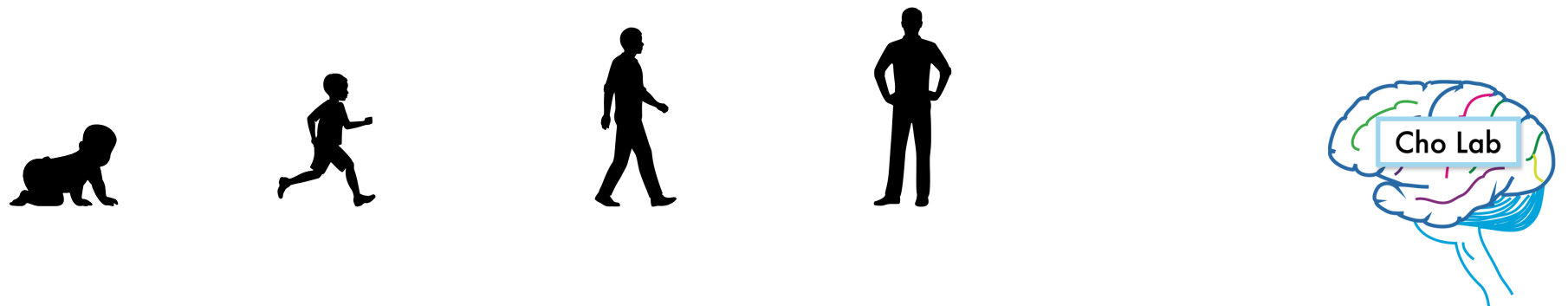
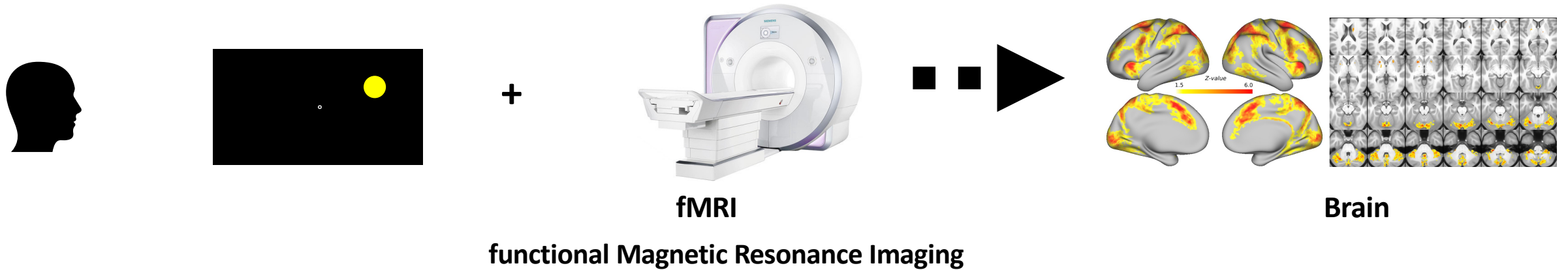


Cortical thinning continues throughout childhood, adolescence and early adulthood, especially in the prefrontal and parietal cortices.

# Motivation and Cognition Change During Development



# Measuring Motivation and Working Memory in the Lab



# Research Study Procedures

## Phone Screen:

This is used to determine eligibility

Ask child and parent about medical, psychiatric history, MRI safety



## Visit 1: Baseline

Consent and Assent to the study  
Clinical assessments/Surveys  
Medical screening  
Cognitive and IQ Testing  
fMRI



## Visit 2 @ 9 mo

Clinical assessments/Surveys  
Medical screening  
Cognitive and IQ Testing

## Visit 3 @ 18 mo

Clinical assessments/Surveys  
Medical screening  
Cognitive and IQ Testing  
fMRI

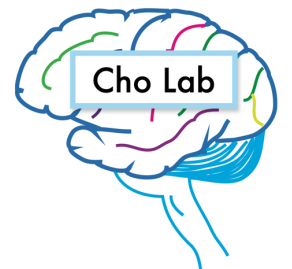


# Measuring Motivation and Working Memory in the Lab

- 13 - 17 years old (with or without depression)
- Able to have an MRI: no braces, claustrophobia or metal implants. Parents are OK with an MRI
- Right-handed

- >20 teens have participated fully in our study, including with our longitudinal follow-up

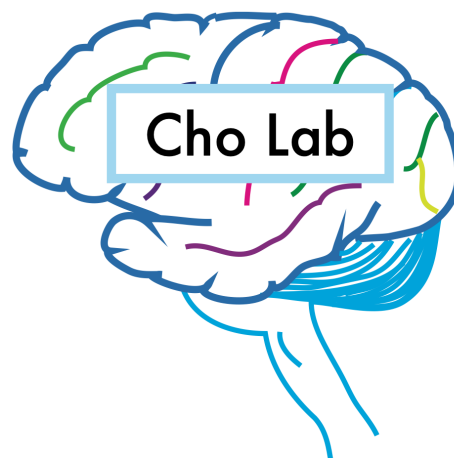
- Teens and families get payment for their time and participation, IQ testing, clinical screening, clinical consultation (if desired)



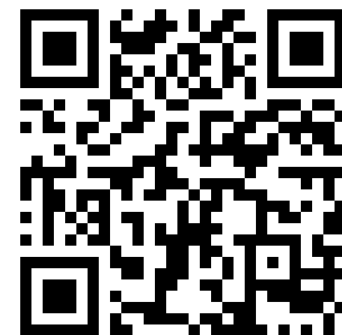
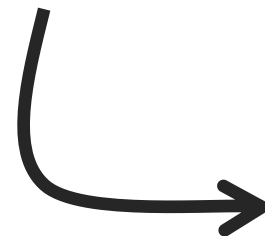
# Thank you!

## Collaborators

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Lab Website at Yale!



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