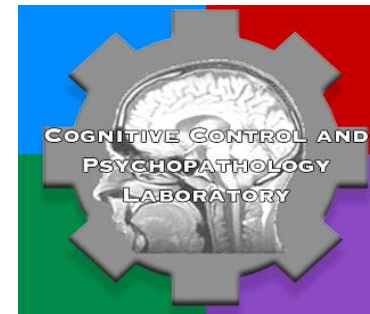


EARLY EMERGENCE OF DEPRESSION:

UNDERSTANDING RISK FACTORS AND TREATMENT

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Characteristics of Preschool Depression

- Depressed preschoolers display “typical” symptoms and signs of Major Depression (MDD) (Luby et al., 2003, Luby et al., 2009).
- Depressed preschoolers show high levels of guilt, loss of pleasure, extreme fatigue, sad/tearful and death thoughts/play (Luby et al., 2003, Luby et al., 2002, Luby et al., 2006)
- Depressed preschoolers are functionally and developmentally impaired (according to parents and daycare/preschool teachers) (Luby et al., 2009)

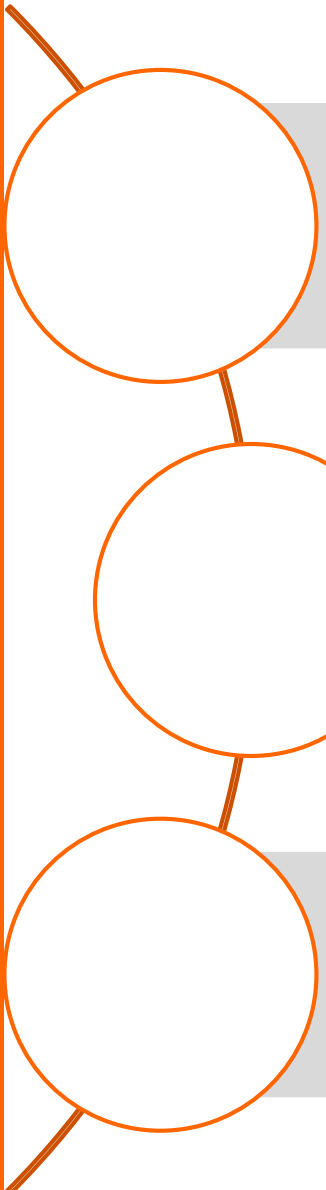


Longitudinal Stability of Preschool MDD

- MDD at preschool age is strong predictor of later MDD
- Family history of affective disorders strong predictor of later MDD
- Preschoolers with MDD have much higher likelihood of later MDD than of other disorders (homotypic continuity)—stays true to form



Brain Imaging in PO-MDD

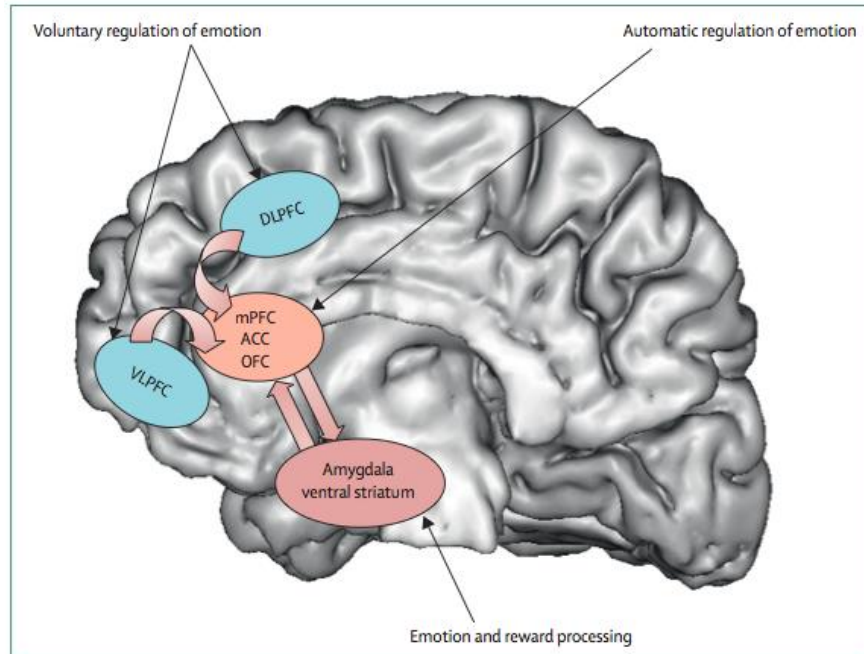


Do children with a history of PO-MDD show changes in brain function and structure that are similar to (or precursors of) those seen in adult MDD?

Do these changes reflect “scars” of MDD or genetic and/or environmental factors that confer risk for PO-MDD?

If risk factors, can we use this information to intervene before the onset of MDD or to predict treatment response?

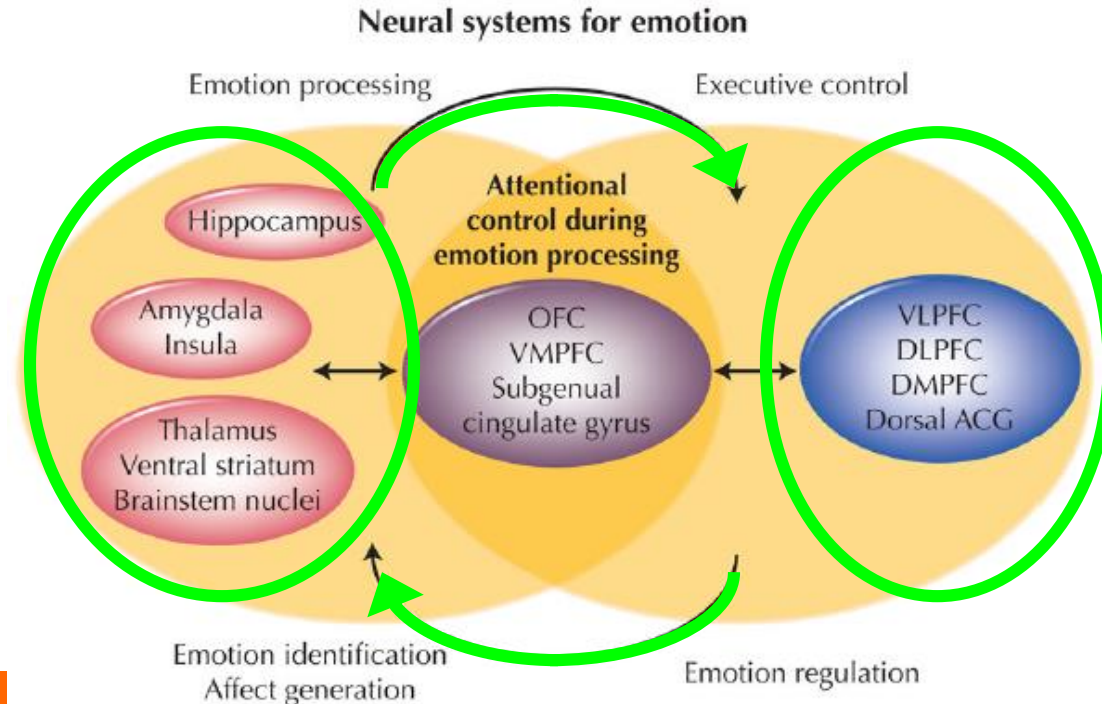
Brain Systems Involved in Adult and Adolescent MDD



Kupfer et al., 2011

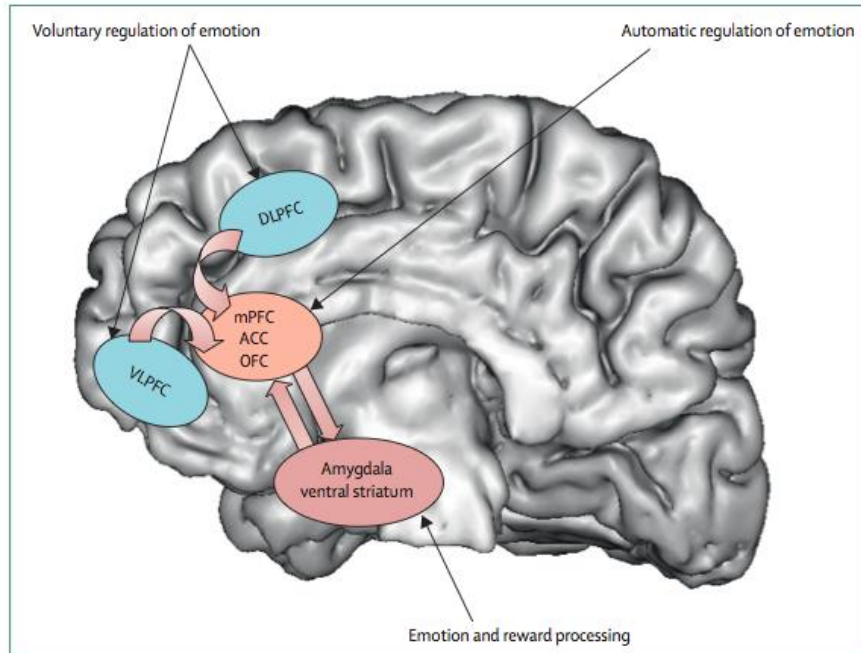
Keener et al., 2009

- ◆ Increased activity in emotion processing regions to negative information (faces, movies, etc.)
- ◆ Decreased “top-down” control over emotion – reduced ability to regulate
- ◆ Abnormal connections between emotion processing and emotion control regions



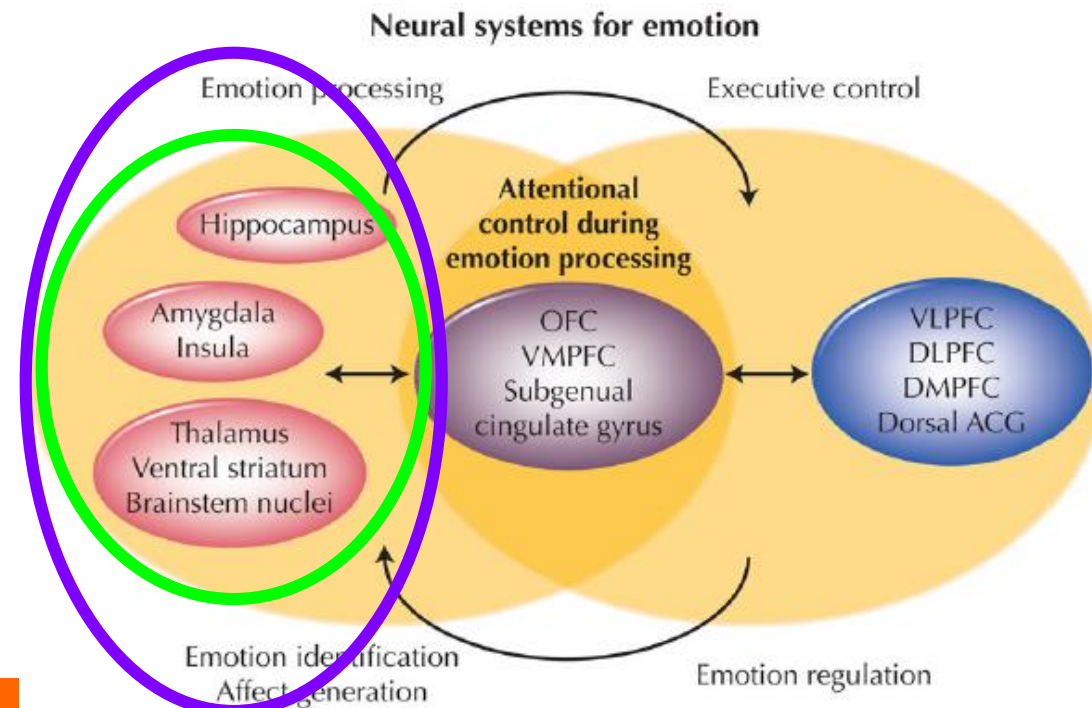
Brain Systems Involved in Adult and Adolescent MDD

- ◆ Do children with a history of PO-MDD show increased activity in emotion processing regions to negative information?



Kupfer et al., 2011

Keener et al., 2009



Preschool Depression Study II- Design

- N=304 preschoolers aged 3-6 ascertained from community
- Over-sampled for preschoolers with symptoms of MDD using a screening checklist (Preschool Feelings).
- Children and caregivers followed over 6+ annual waves of data collection
- Semi-structured diagnostic interviews that included expanded MDD and Mania sections.
- Started imaging at Waves 4 &5, when children were 8-10
 - Also have new studies imaging children who are still preschool age



Gender Judgments of Emotional Faces

Neutral



Sad



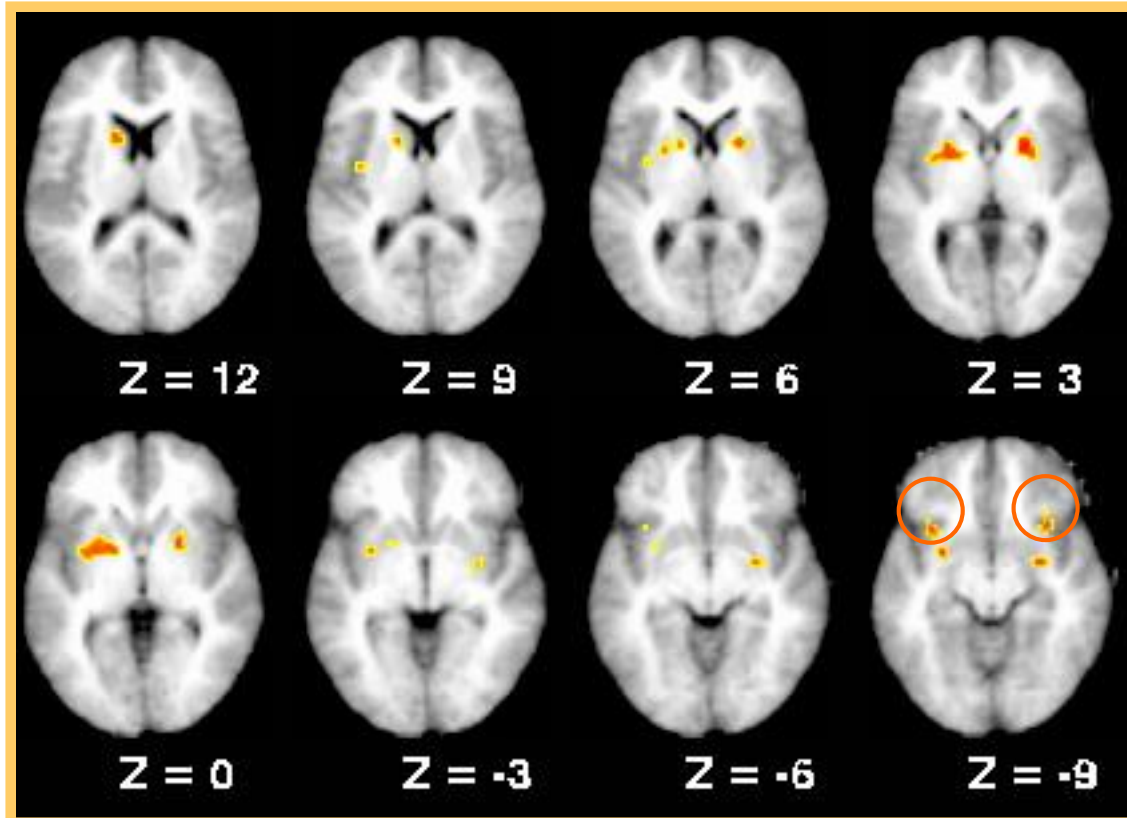
Happy



Fear



Depression severity from initial evaluation at Preschool age



Orbital Frontal Cortex

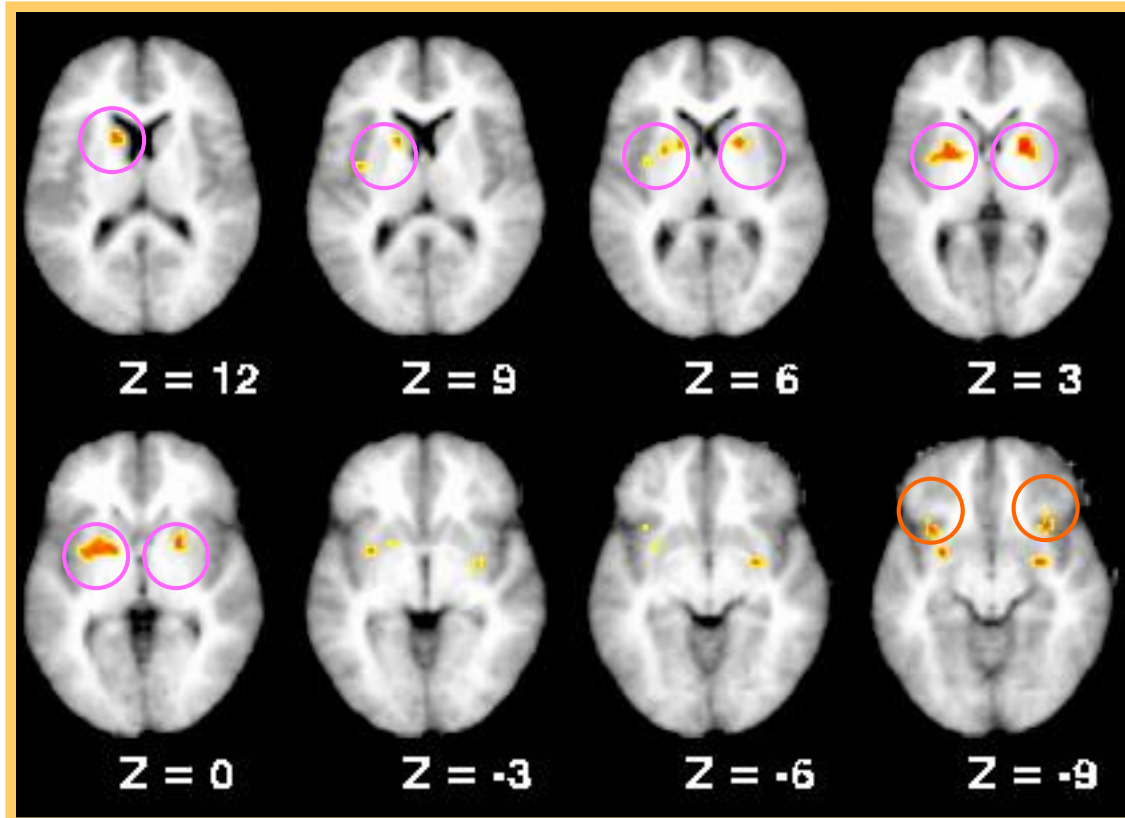
Activation
to Sad
Faces

Correlations remain when you covary for:

- Comorbid Internalizing
- Comorbid Externalizing
- CDI Scores (parent and child) at the time of scan

Barch et al., 2013

Depression severity from initial evaluation at Preschool age



Activation
to Sad
Faces

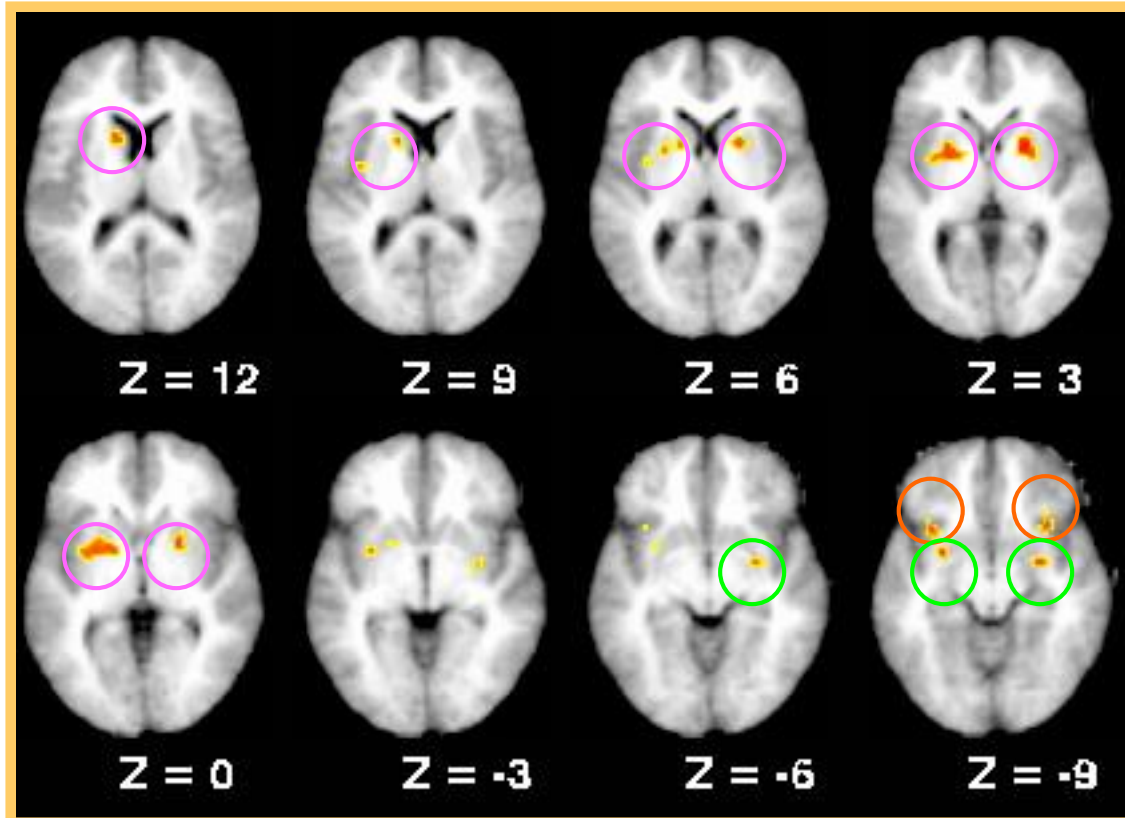
Correlations remain when you covary for:

- Comorbid Internalizing
- Comorbid Externalizing
- CDI Scores (parent and child) at the time of scan

Orbital Frontal Cortex Striatum

Barch et al., 2013

Depression severity from initial evaluation at Preschool age



Activation
to Sad
Faces

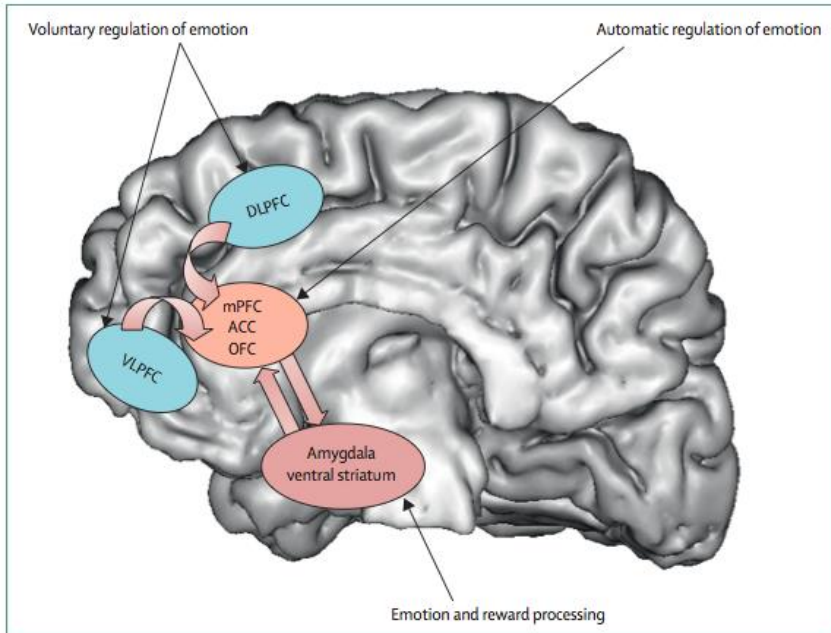
Correlations remain when you covary for:

- Comorbid Internalizing
- Comorbid Externalizing
- CDI Scores (parent and child) at the time of scan

Orbital Frontal Cortex Striatum Amygdala

Barch et al., 2013

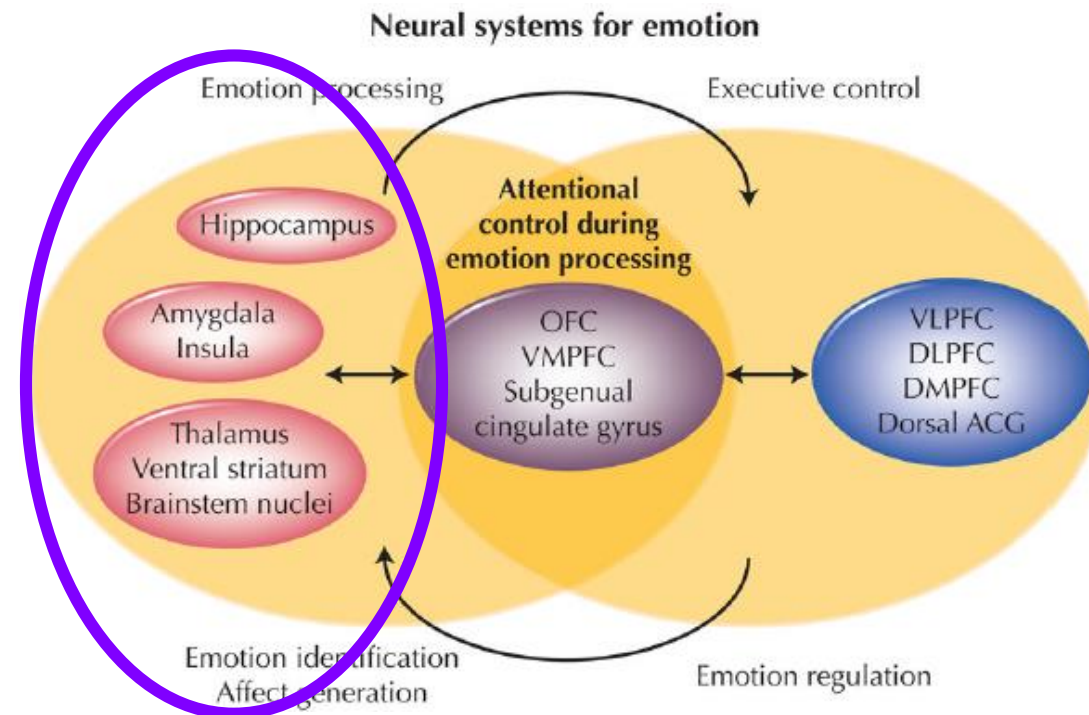
Brain Systems Involved in Adult and Adolescent MDD



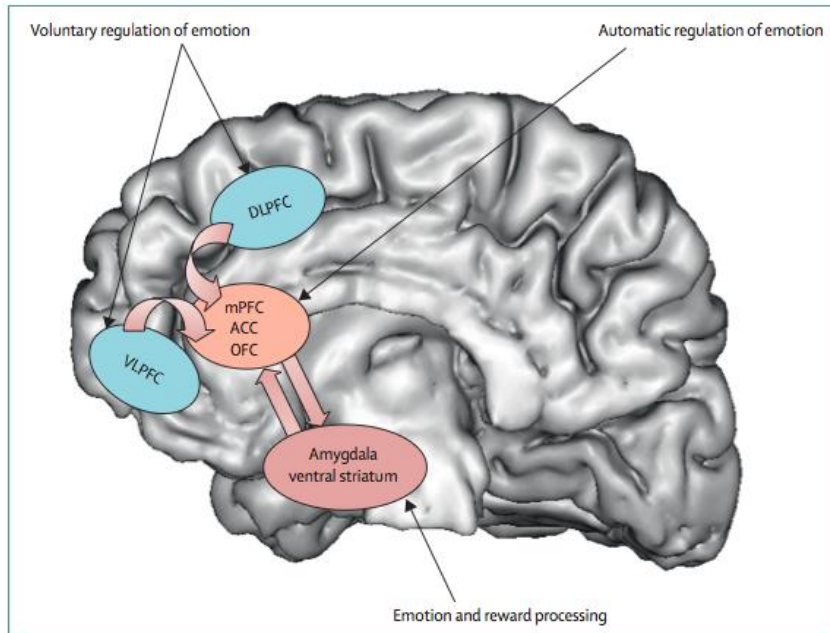
Kupfer et al., 2011

- ◆ Children with a history of PO-MDD DO show increased activity in emotion processing regions to negative information

Keener et al., 2009



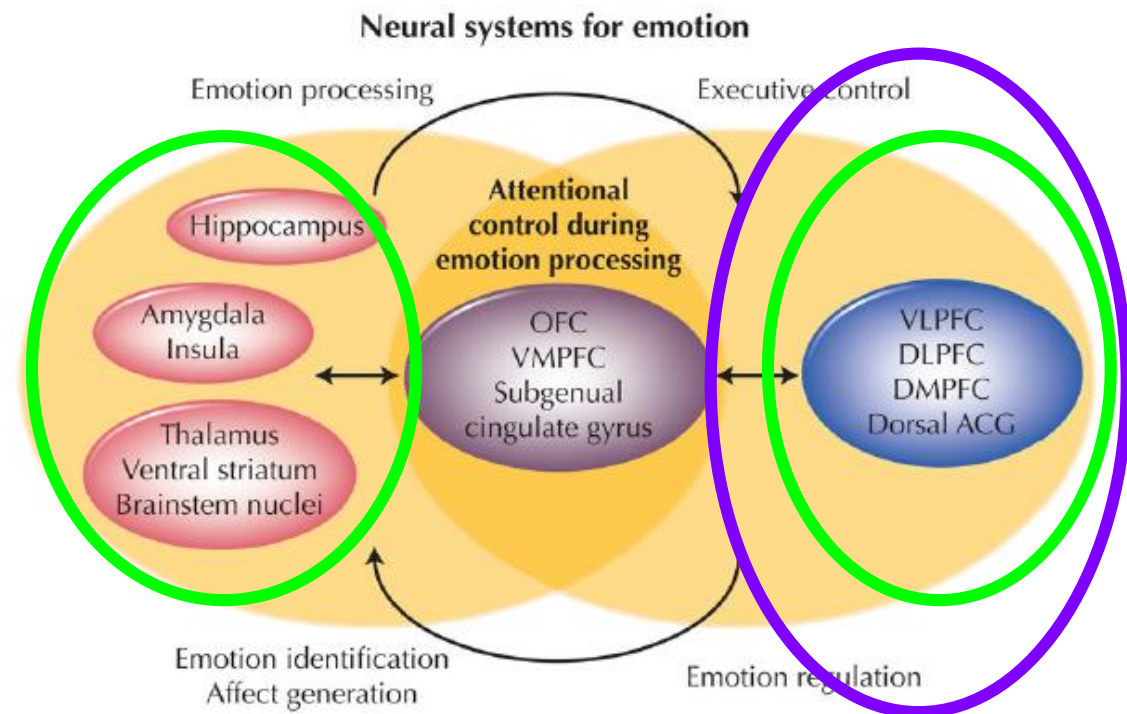
Brain Systems Involved in Adult and Adolescent MDD



Kupfer et al., 2011

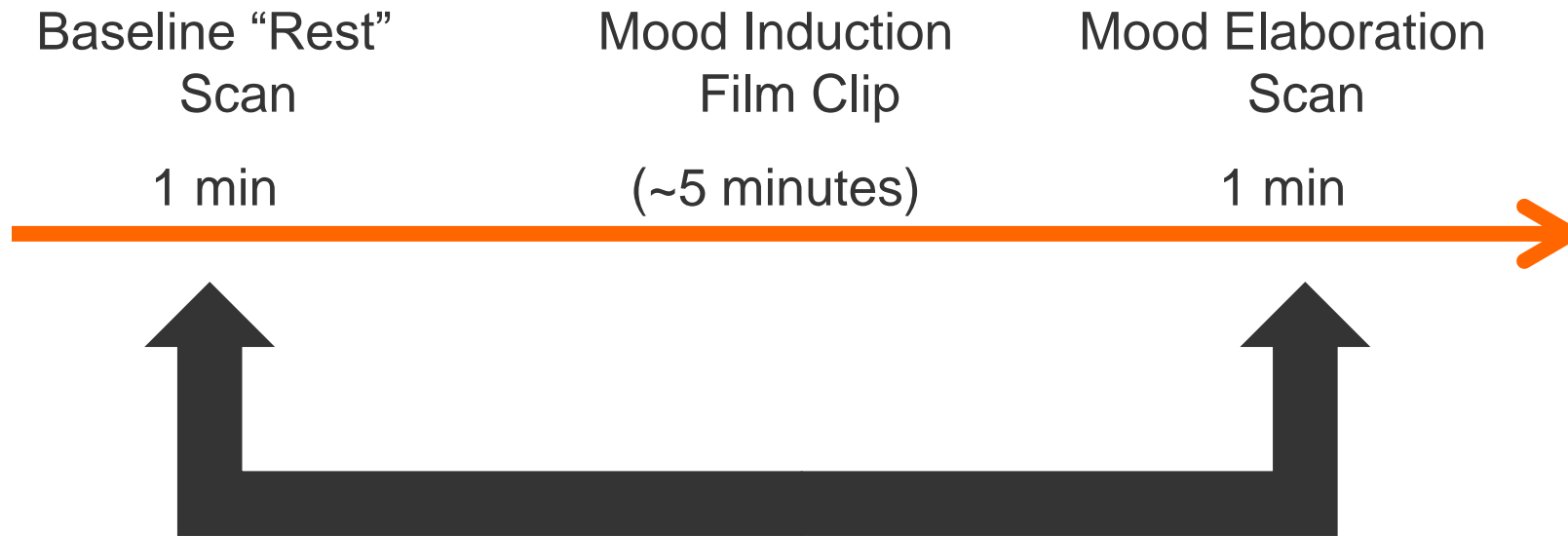
- ◆ Do children with a history of PO-MDD show decreased “top-down” control over emotion processing?

Keener et al., 2009



Mood Regulation

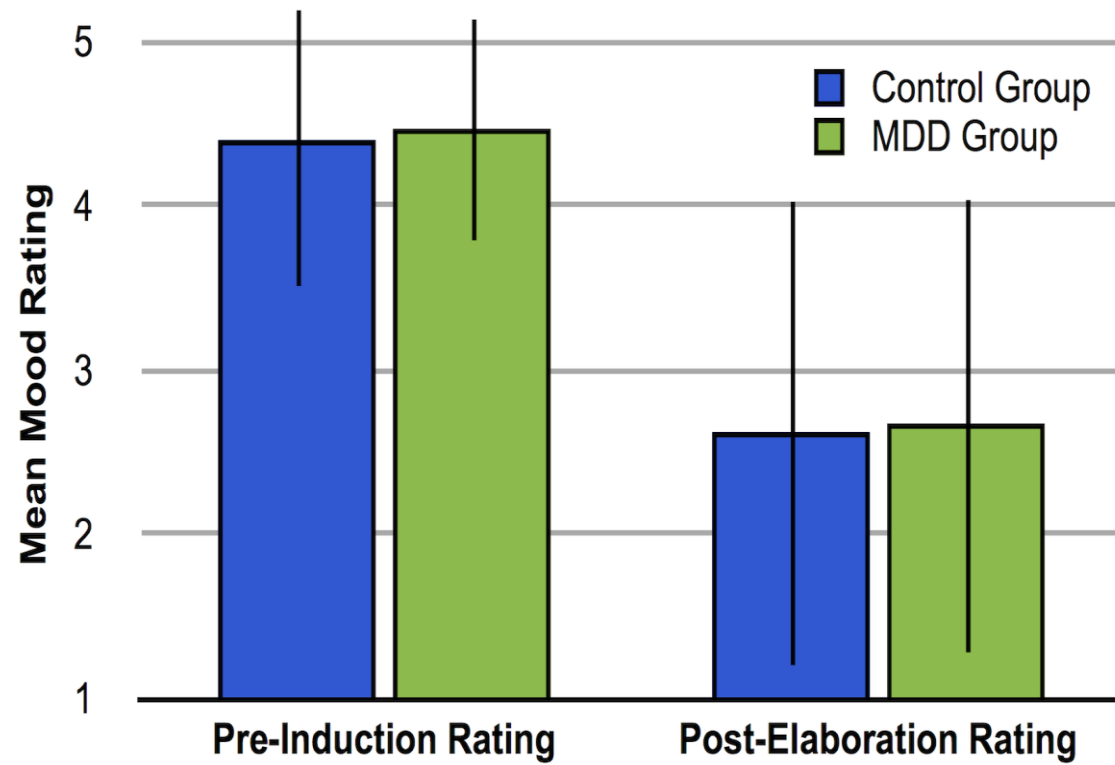
Paradigm Developed by Collaborator Ian Gotlib at Stanford



Pagliaccio et al, 2012



Mood Induction

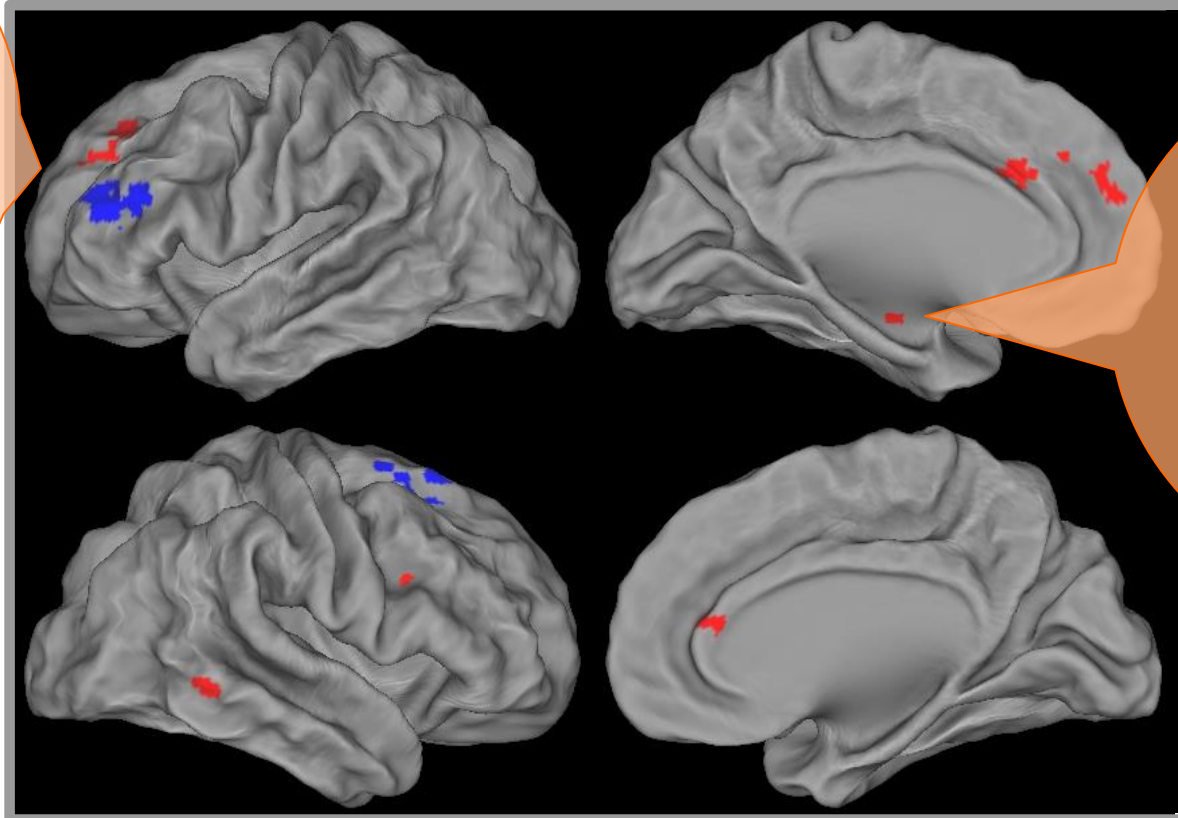


Pagliaccio et al, 2012

Mood Induction

Dorsal PFC

Less activity in
MDD children
and with higher
MDD severity



AMYGDALA

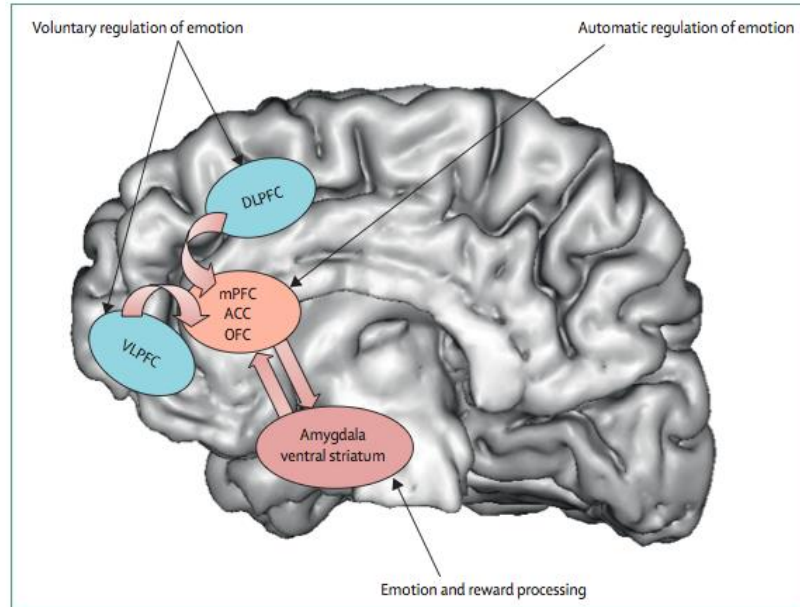
Greater activity with
higher depression
severity at time of
scan

Regions of interest found in categorical and dimensional analysis of the relation between depression and brain activity during sad mood elaboration. Blue regions are those that showed diagnostic group differences in the categorical analyses. Red regions are those that showed significant correlations with current depression scores (CDI).



Pagliaccio et al, 2012

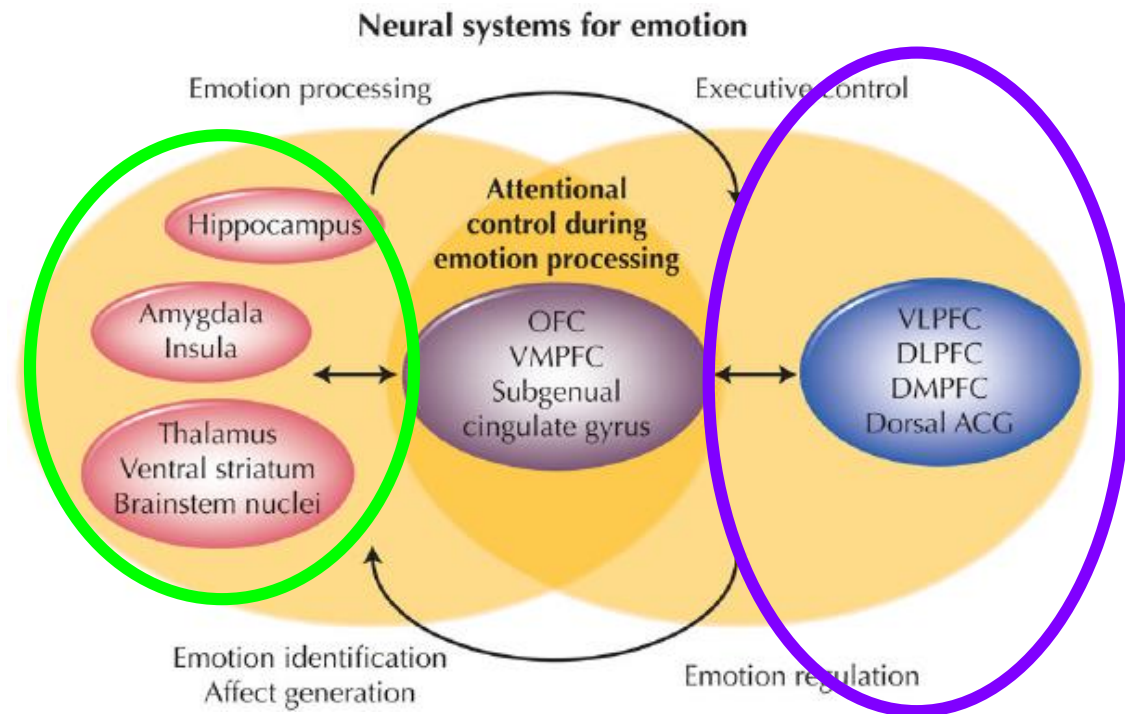
Brain Systems Involved in Adult and Adolescent MDD



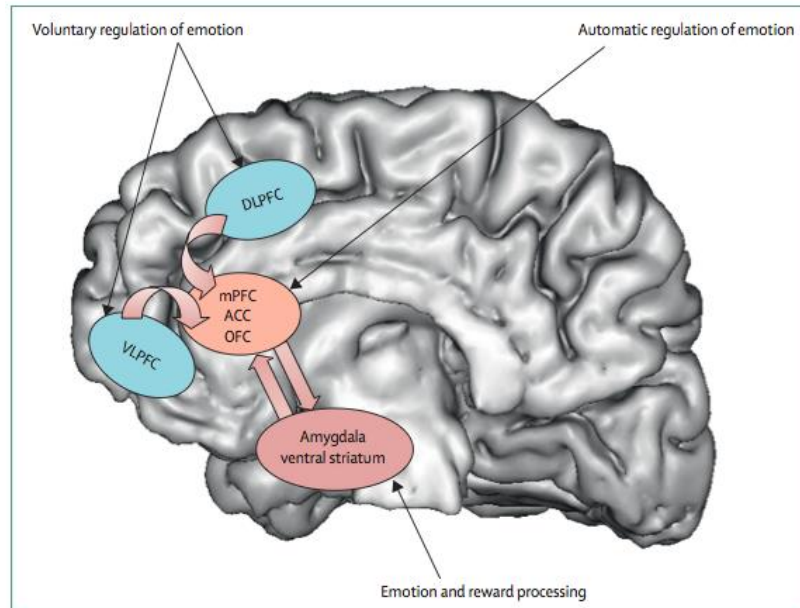
Kupfer et al., 2011

◆ PO-MDD children DO show decreased “top-down” control over emotion processing

Keener et al., 2009



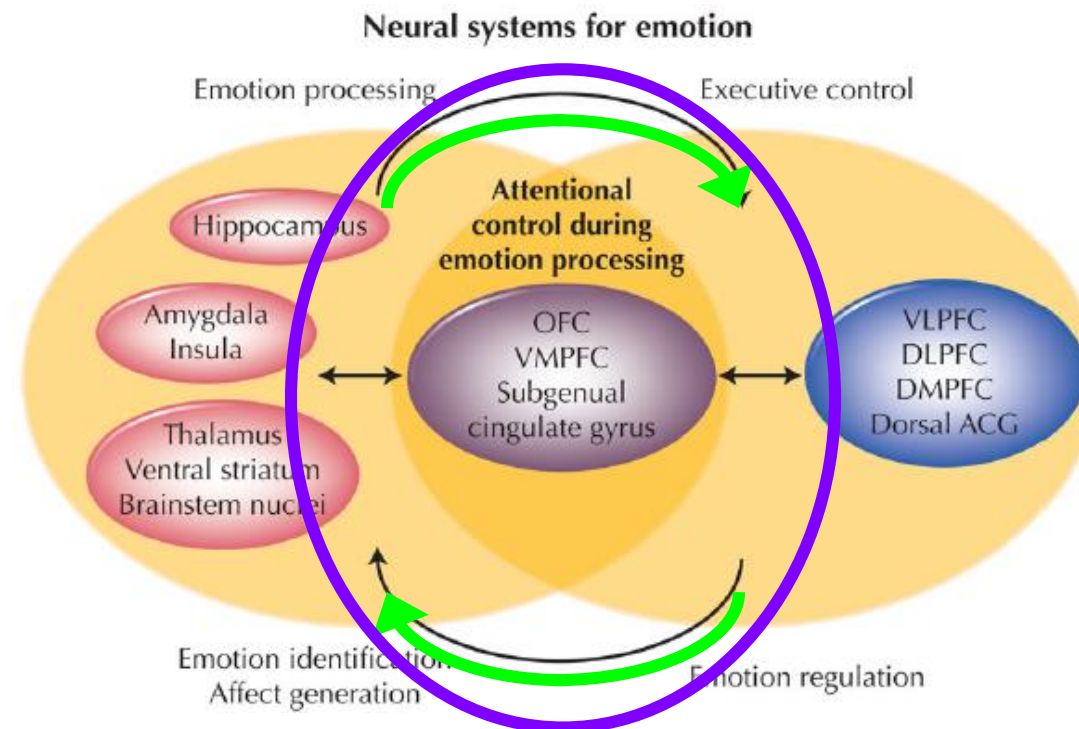
Brain Systems Involved in Adult and Adolescent MDD



Kupfer et al., 2011

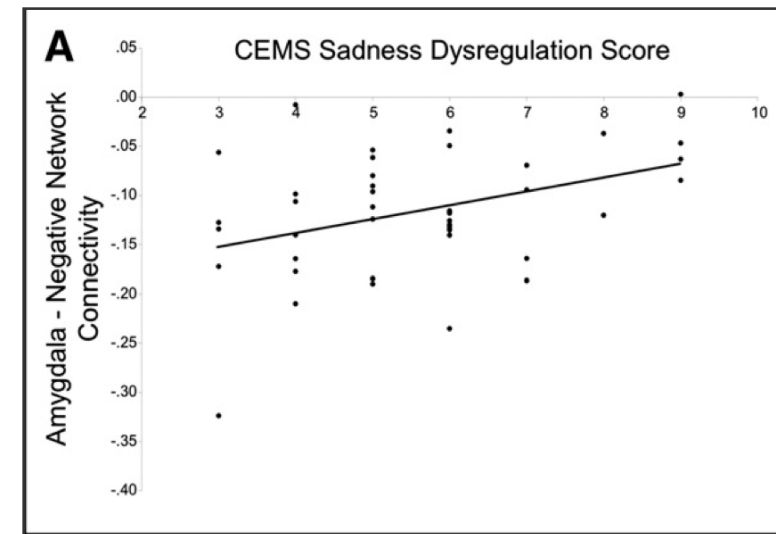
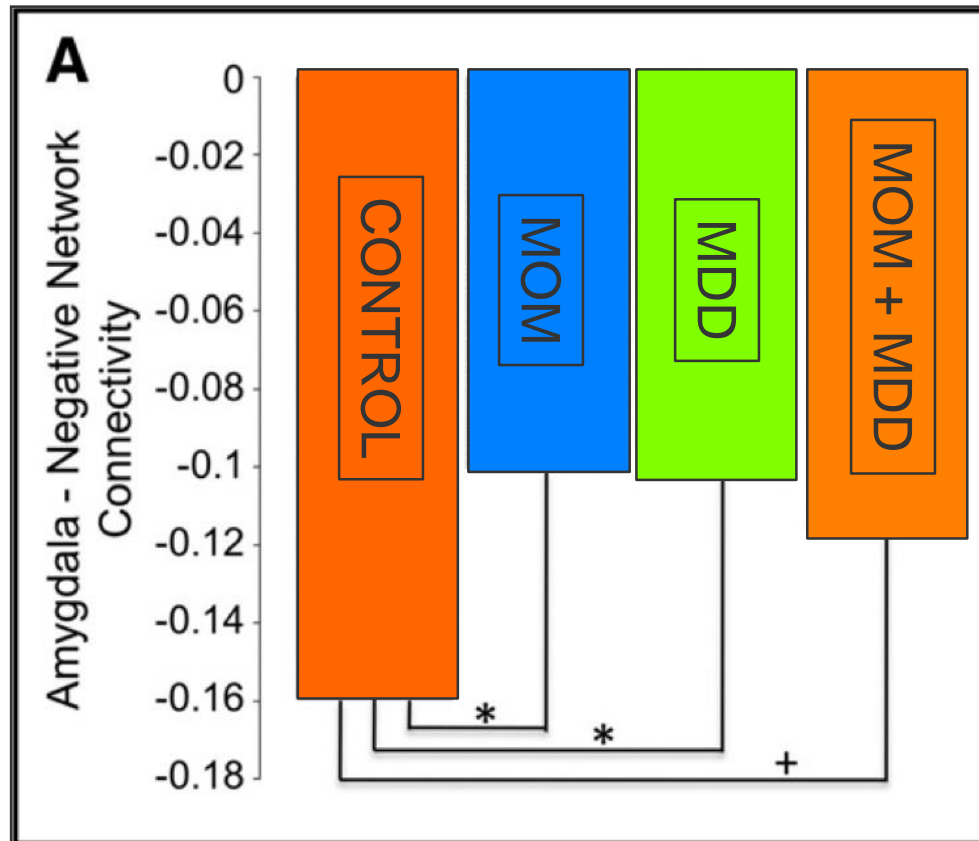
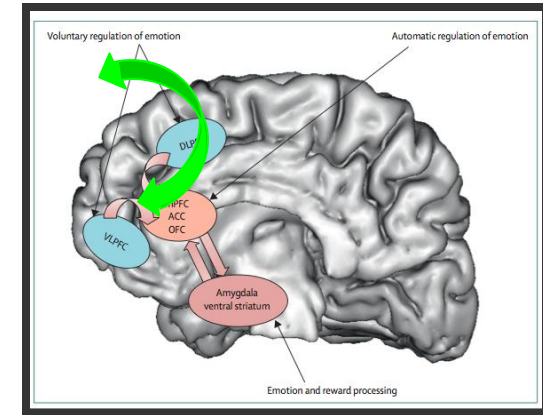
- ◆ Do PO-MDD children show abnormal connectivity between emotion processing and emotion control regions?

Keener et al., 2009



Amygdala Functional Connectivity and Depression Risk

Reduced “coupling” between emotion regulation and emotion processing regions



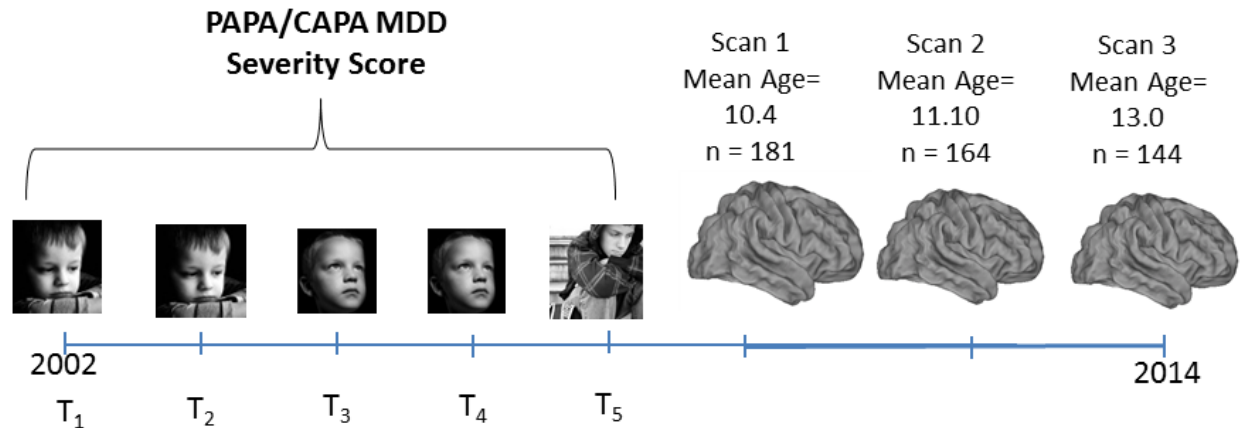
Luking et al., 2011



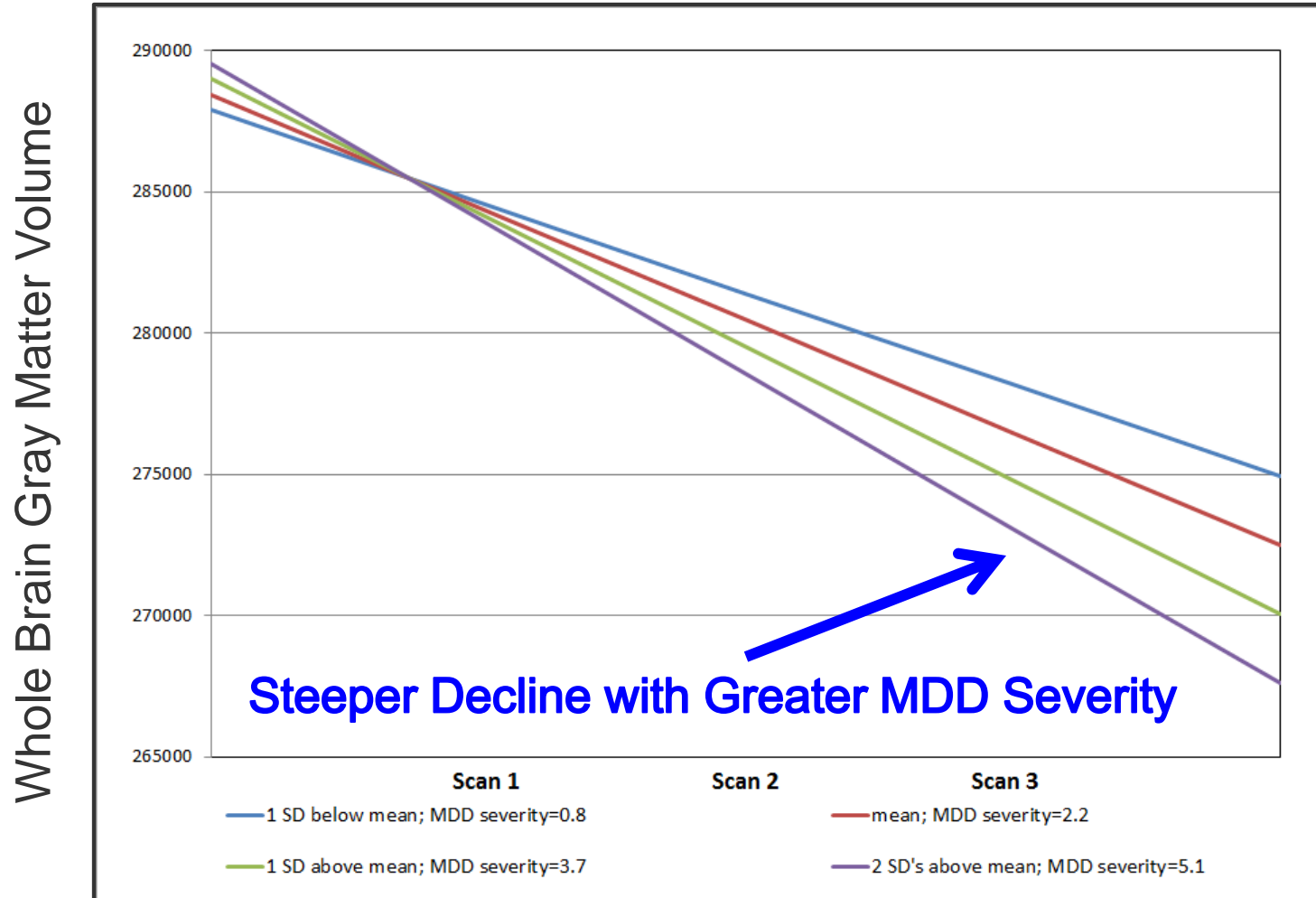
**What about broader effects
on neurodevelopment?**

Early Childhood MDD Predicting Trajectory of Brain Development in Middle Childhood-Early Adolescence

Multi-level Modeling: MDD predicting Brain Changes Across Scan Waves



More severe MDD in preschool and early childhood predicts greater loss of gray matter volume at later school age



Treatment for PO-MDD: Why and How?

- Alterations in structure/function of brain emotion processing regions in PO-MDD acutely and children with history of PO-MDD
- Genetic and psychosocial factors are risk factors for MDD
- Psychosocial factors powerfully influence brain development
- Early psychosocial interventions focused on emotion development promising

Parent-Child Interaction Therapy – Emotion Development

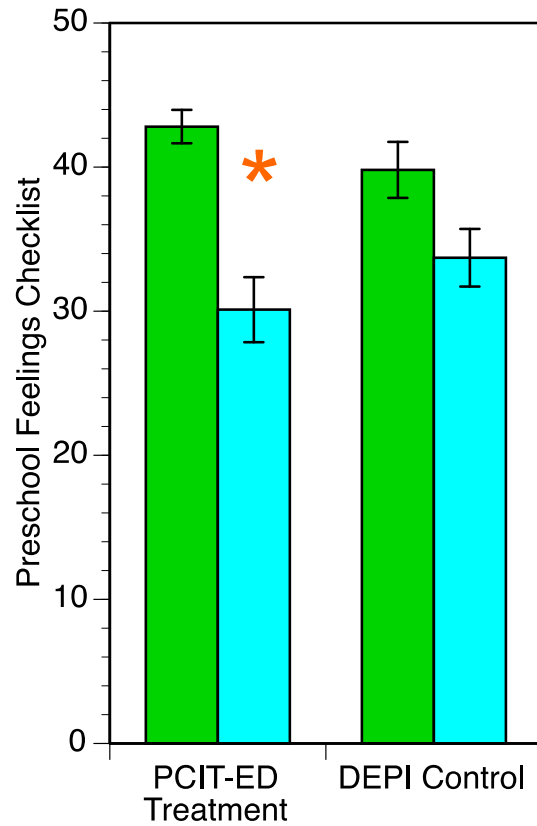
- Uses principles and techniques such as “bug in the ear”, parenting style, and homework
- Addresses problems in patterns of emotional reactivity
- Focuses on parent’s role as emotion regulator for their child
- Uses emotionally evocative tasks in the session
- Focuses on helping young children to develop emotionally, both in terms of enhancing positive emotions and regulating negative emotions



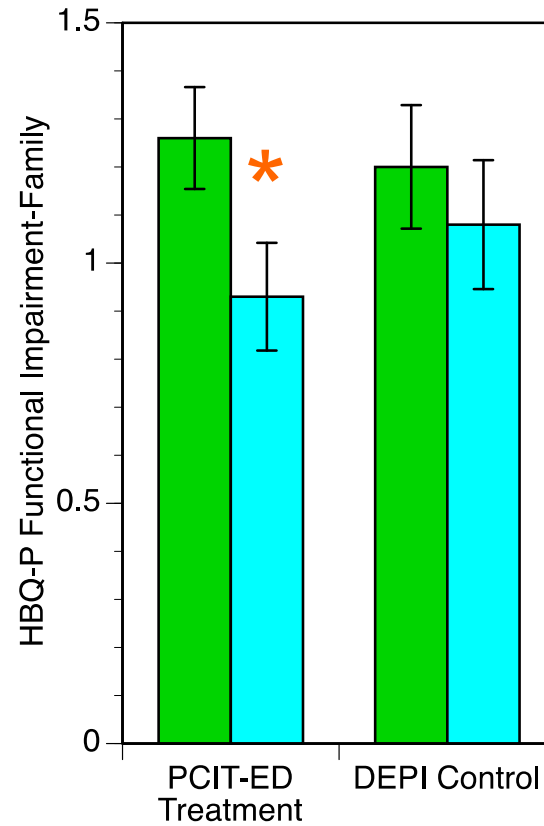
WUSTL PCIT-ED Treatment Study



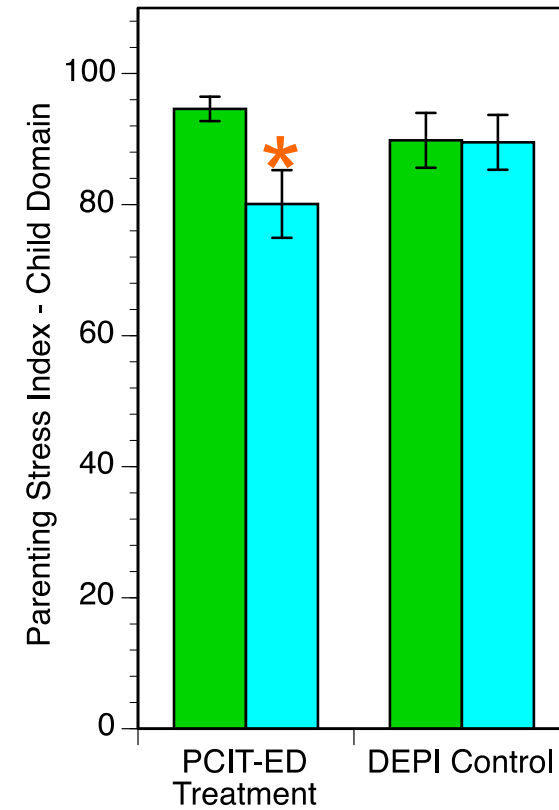
Promising Results from Pilot Study



Child Depression



Family Impairment



Parenting Stress

■ Pre-Treatment ■ Post-Treatment

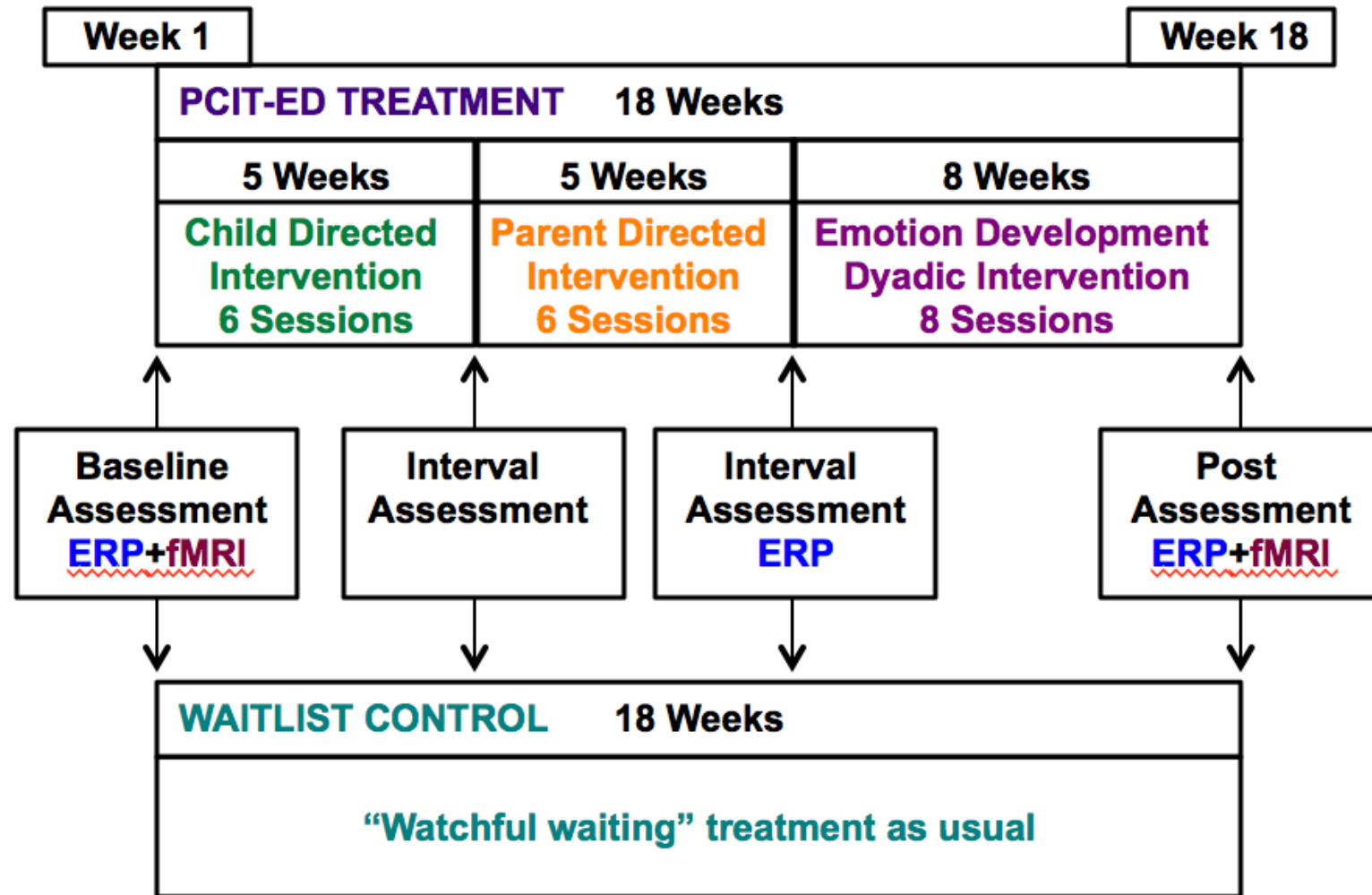


New Large Scale Randomized Clinical Trial Integrating Neural Predictors

- Does brain structure or function predict which children will or will not benefit from PCIT-ED?
- Do changes in brain function and structure during PCIT-ED tell us about the *mechanisms* of change?
- Elucidating brain change more powerfully impacts public policy

Study Design

Timing of ERP and fMRI assessments in relation to PCIT-ED Treatment and Assessments



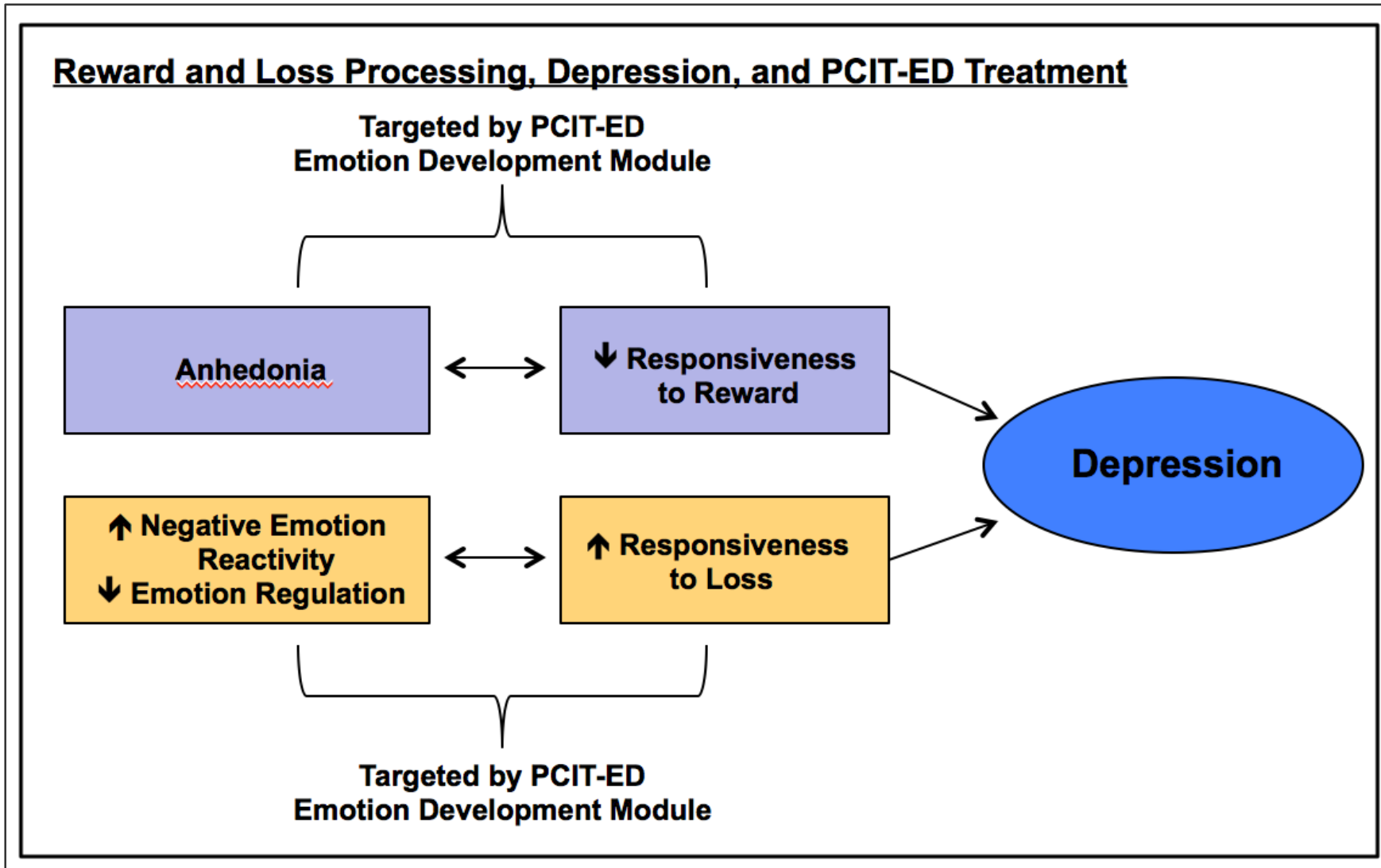
fMRI of Emotion and Reward Processing



ERP of Emotion and Reward Processing



Targeting Positive and Negative Emotion Processing Systems in PO-MDD



Conclusions & Future Directions

- Children with a history of PO-MDD show changes in brain function and structure similar to those seen in adult MDD
 - ↑ activity of regions involved in emotion processing (e.g., amygdala)
 - ↓ activity of regions involved in emotion regulation
 - ↓ connectivity b/w emotion processing & emotion regulation regions
 - ↑ whole brain gray matter decline over development
- Do these changes reflect “scars” of MDD or genetic and/or neurodevelopmental factors that confer risk for PO-MDD?
 - Some evidence that these are not just scars, but also associated with risk
- If risk factors, can we use this information to treat PO-MDD or even intervene before the onset of MDD?
 - **STAY TUNED FOR RESULTS OF PCIT-ED STUDY!**