Developmental Considerations in the Neurobiology of Psychiatric Disorders

Outline

- Developmental psychopathology broadly considered
- Temperament
- Child and adolescent psychopathology
- Research on face perception
- The impact of early life stress

What is Developmental Psychopathology?

- Childhood psychopathology
- Adolescent psychopathology
- Risk factors for psychopathology

- Psychopathology across the life span

- "The study of the origins and course of individual patterns of behavior maladaptation" (Sroufe & Rutter)
  - Factors contributing to resilience and adaptive functioning too

What is Developmental Psychopathology?

- Longitudinal course
- Comorbidity
- Functional concomitants (e.g., interpersonal problems)
- Familial context (e.g., positive family history of depression)
- Genetic studies (e.g., twin studies, molecular genetics)
- Psychosocial studies (e.g., family discord, expressed emotion)
- Psychological context (e.g., emotion regulatory problems, stress sensitivity)

Miller (2007) *Brain & Cognition*

- Cultural and socioeconomic context; life stress, trauma, and various forms of abuse; social support and validation

What is Temperament?

- "Stable moods and behavioral profiles observed in infancy and early childhood" (Kagan)
- Biologically based individual differences in behavior and affect that are stable across time and situation (Goldsmith)

The Neurobiology of Child and Adolescent Psychopathology

- Depression
- Anxiety
- PTSD

- ADHD
- Conduct Disorder

- Autism
- Other Pervasive Developmental Disorders

- Internalizing vs. Externalizing Disorders
- Behavioral Inhibition

Main components and function of the triadic modules.

Modules of the triadic model		
Approach	Avoidance	Regulation
Main structures		
Striatum	Amygdala	Dorsolateral PFC
Orbitofrontal cortex	Hippocampus	Ventromedial Orbital PFC
	Insula	Anterior cingulate cortex
Function		
Appetitive stimuli	Aversive stimuli	Salience detection
Valence/salience value	Valence/salience value	Executive attention
Motivation	Fear responses	Motor control
Motor response	Threat avoidance	Conflict detection
Positive affect	Negative affect	Conflict monitoring
		Conflict resolution

Ernst (2014) *Brain and Cognition*

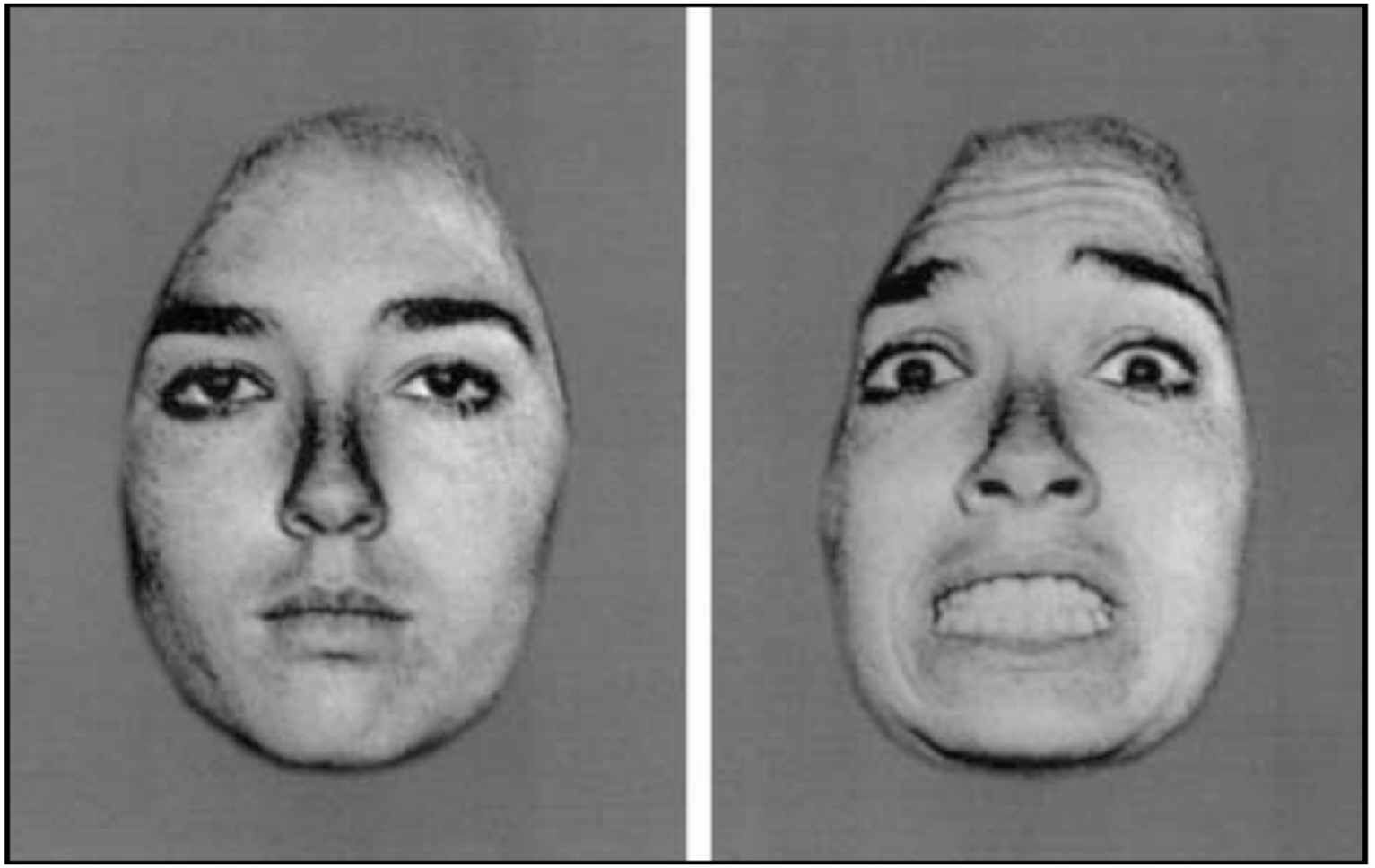


Figure 1. Examples of neutral and fearful expressions used in the passive-viewing task.[41]

Thomas et al. (2001) ***Archives of General Psychiatry***

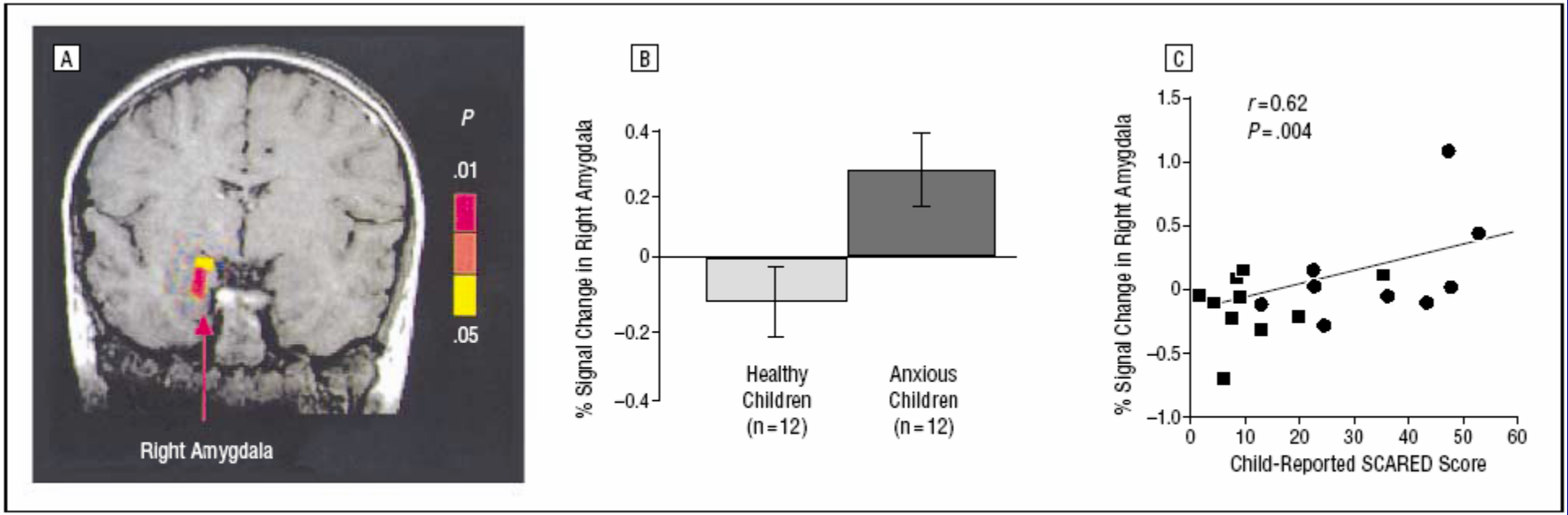


Figure 2. A, Significant region of the right amygdala (x=11, y=– 7, z=–14) observed in the diagnosis (anxious vs healthy children) × condition (fearful vs neutral faces) interaction. B, Percent change in normalized magnetic resonance signal intensity in the right amygdala for the comparison between fearful and neutral faces for anxious and healthy children. Bars reflect the SEM. C, Correlation between the percent change in normalized magnetic resonance signal intensity in the right amygdala and the child-reported score from the Screen for Child Anxiety Related Emotional Disorders (SCARED). Squares reflect healthy children (n=9); circles reflect children with generalized anxiety and/or panic disorder (n=10).

Thomas et al. (2001) ***Archives of General Psychiatry***

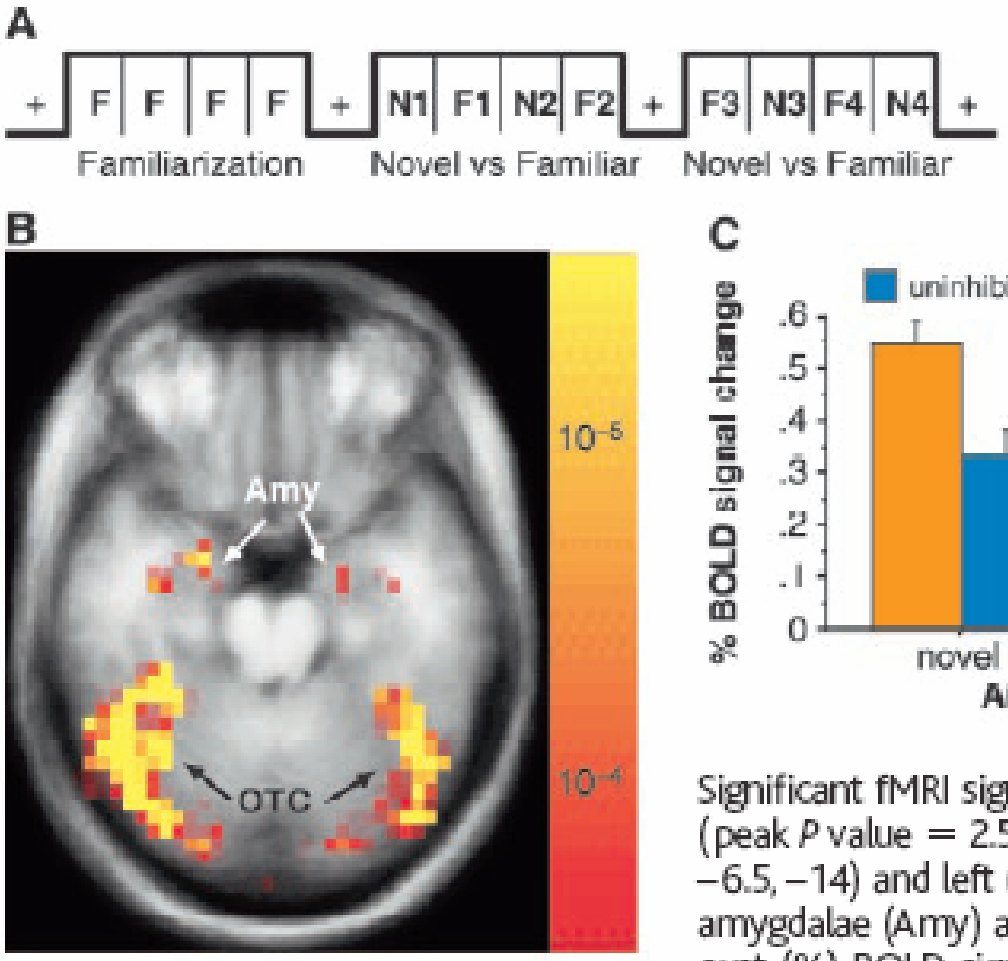


Fig. 1. (A) The presentation of stimuli was divided into two phases: a familiarization phase and a test phase that consisted of alternating 24-s blocks of either novel (N) or familiar (F) faces with neutral expression. Subjects viewed a fixation cross (+) during 24-s fixation blocks. (B) Colorized group statistical map superimposed on coronal group-averaged T1 structural image in Talairach space. Significant fMRI signal changes (arrows) are shown in the right (peak P value $= 2.5 \times 10^{-5}$; Talairach coordinates $x, y, z = 21, -6.5, -14$) and left ($P = 4.2 \times 10^{-4}$; $x, y, z = -21.5, -6.7, -18$) amygdalae (Amy) and occipito-temporal cortex (OTC). (C) Percent (%) BOLD signal change (versus fixation) in amygdala to novel versus familiar faces in adult subjects who were inhibited and uninhibited in the second year of life. One standard error of the mean is indicated.

Schwartz et al. (2003) *Science*

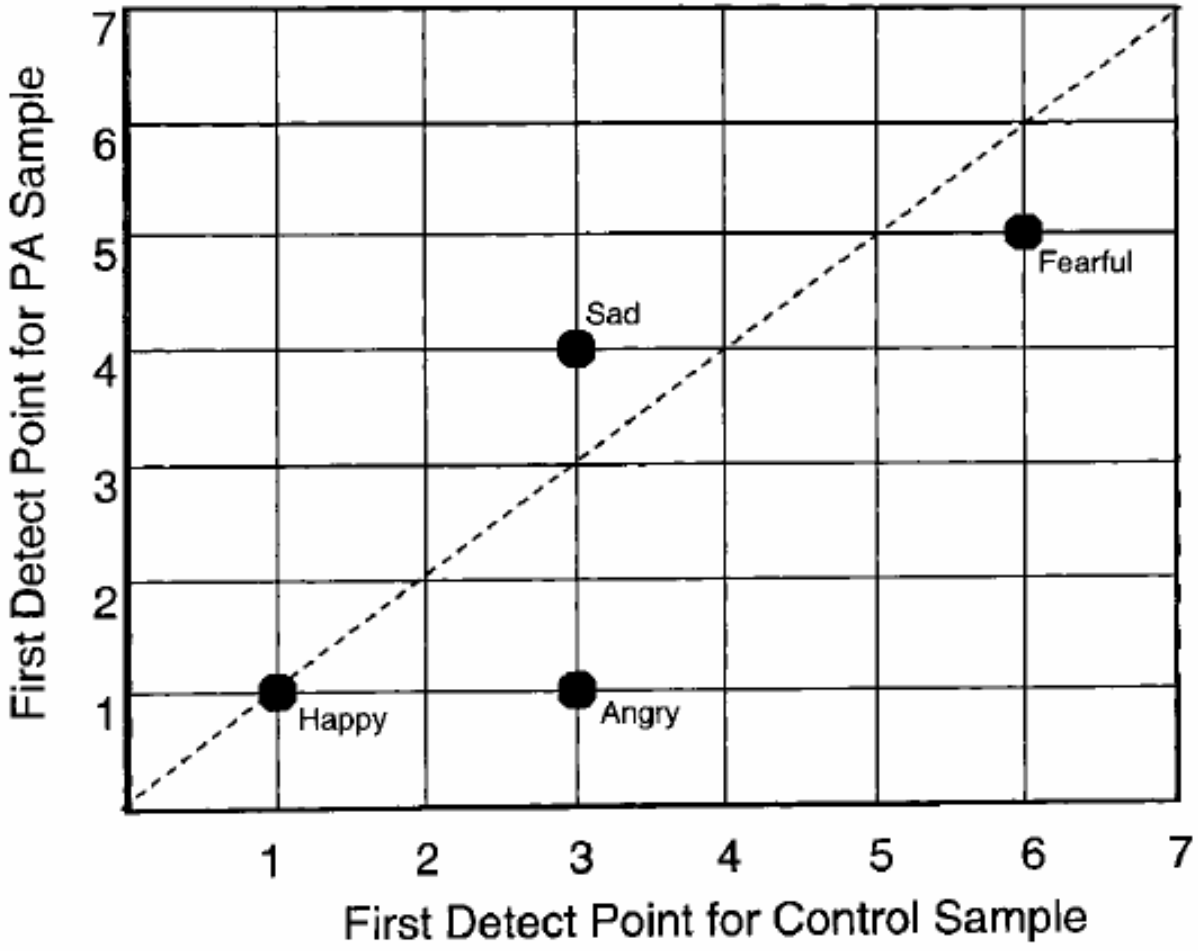


Figure 7. First point of detection for happy, angry, sad, and fearful faces by physically abused (PA; y-axis) and control (x-axis) children. Points that lie on the slope reflect no differences between groups. Emotions that physically abused children detected sooner than controls lie below the slope line, whereas emotions detected sooner by controls lie above the line.

Pollak & Sinha (2002) ***Developmental Psychology***

- **Coe et al. (2003) – Mild prenatal stress effects (10-min separation with 3 loud noise bursts, 5 days/wk, 6 wks) at age 2-3 yrs**
  - **Behavior: decreased focused exploration, increased nondirected locomotor behavior (e.g. pacing)**
  - **Higher cortisol levels (basal levels and following DST)**
  - **Reduced hippocampal volume (10-12%)**
  - **Reduced neurogenesis (32%) (no effect on neuronal maturation)**
- **Parker et al. (2004, 2006) – Mild postnatal stress effects (1-hr separation per wk, 5 wks) at age 50 wks**
  - **Behavior: decreased maternal clinging, enhanced exploratory and play behaviors, and increased food consumption**
  - **Lower basal plasma ACTH and cortisol concentrations**
  - **Lower ACTH and cortisol responses to novel environment**
- **Implications for psychopathology and resilience??**

nature neuroscience

Allele-specific *FKBP5* DNA demethylation mediates gene–childhood trauma interactions

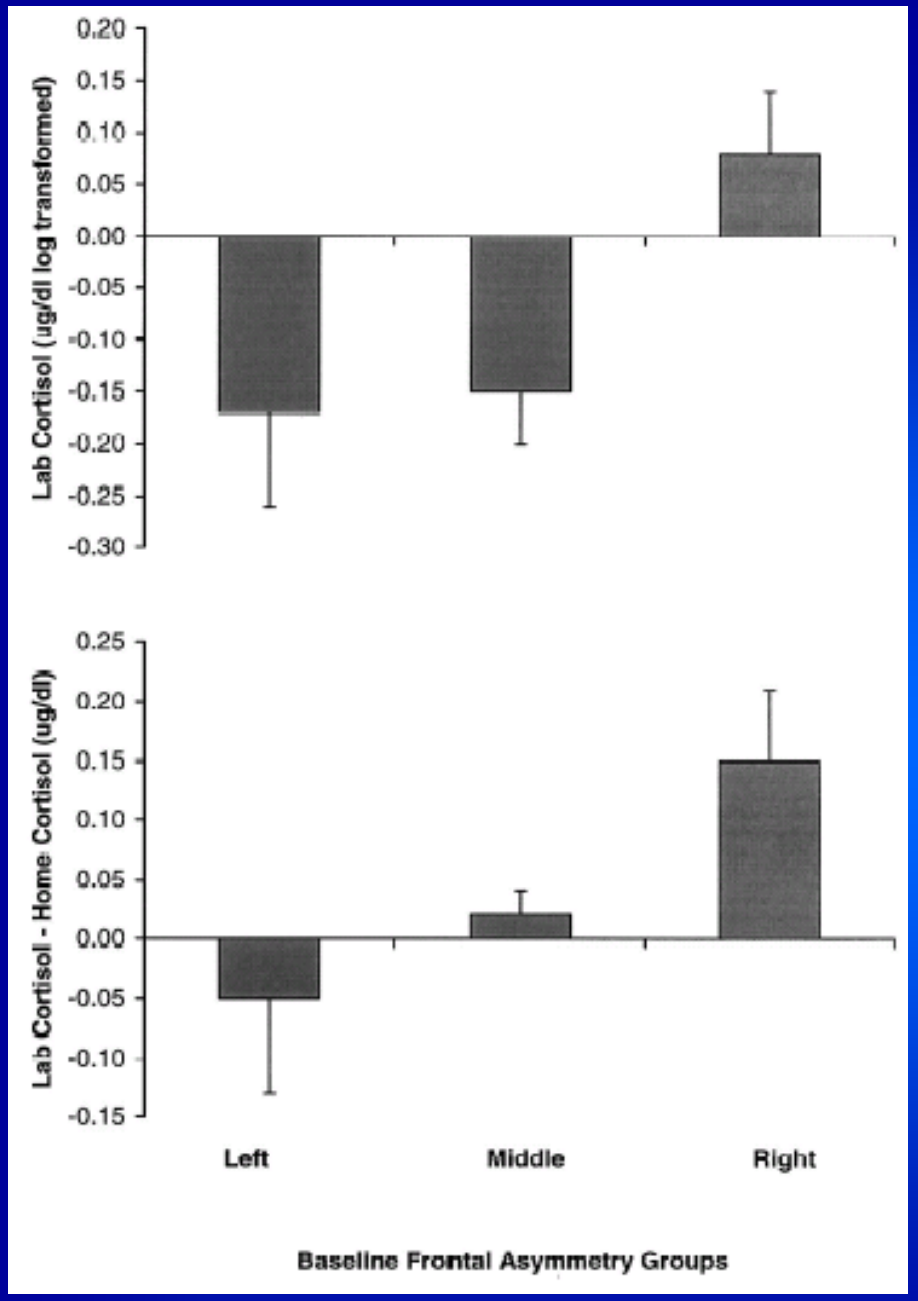
Torsten Klengel[1], Divya Mehta[1], Christoph Anacker[2], Monika Rex-Haffner[1], Jens C Pruessner[3], Carmine M Pariante[2], Thaddeus W W Pace[4], Kristina B Mercer[5], Helen S Mayberg[4], Bekh Bradley[4,6], Charles B Nemeroff[7], Florian Holsboer[1], Christine M Heim[4,8], Kerry J Ressler[4,5,9], Theo Rein[1] & Elisabeth B Binder[1,4]

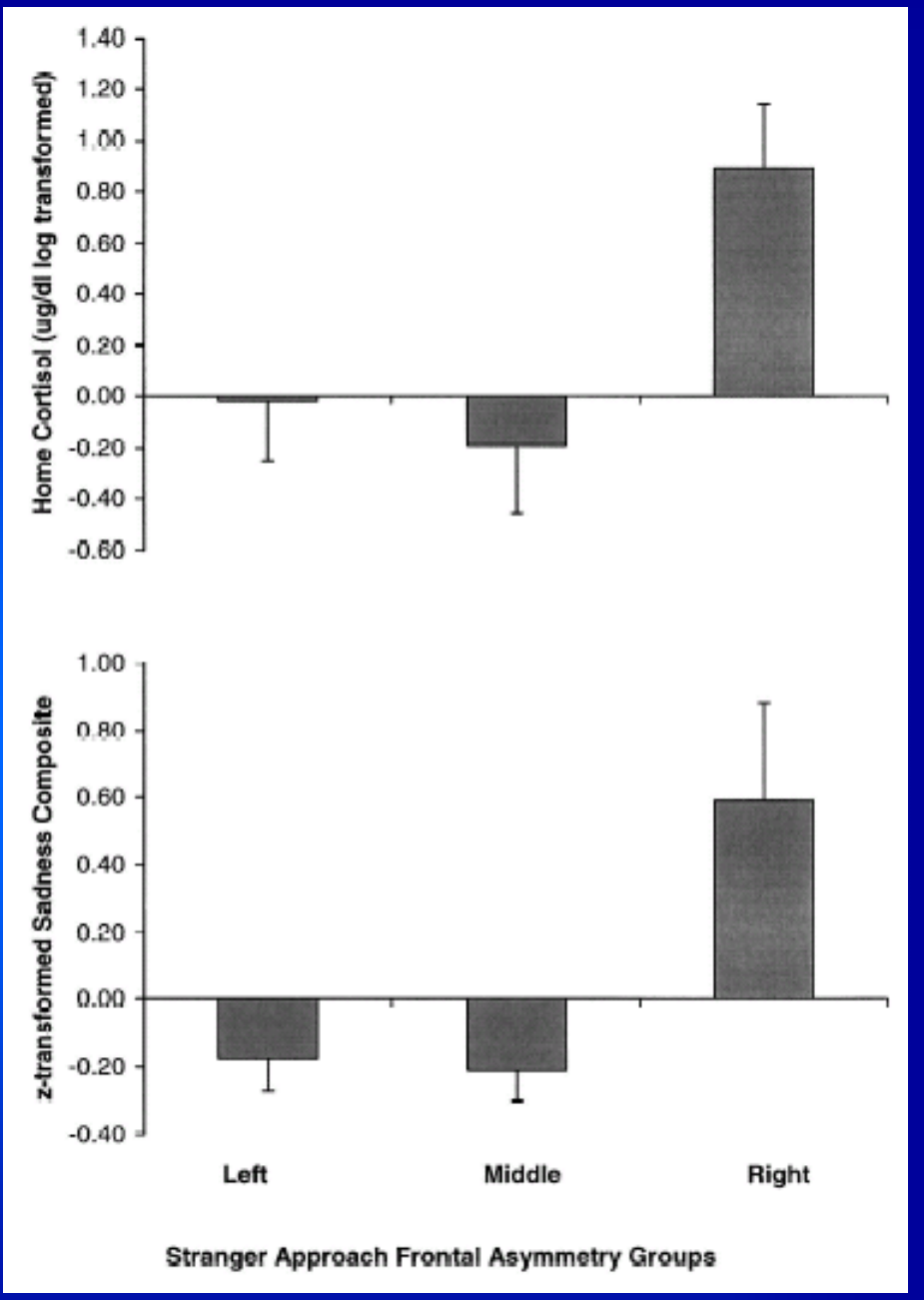
Although the fact that genetic predisposition and environmental exposures interact to shape development and function of the human brain and, ultimately, the risk of psychiatric disorders has drawn wide interest, the corresponding molecular mechanisms have not yet been elucidated. We found that a functional polymorphism altering chromatin interaction between the transcription start site and long-range enhancers in the FK506 binding protein 5 (*FKBP5*) gene, an important regulator of the stress hormone system, increased the risk of developing stress-related psychiatric disorders in adulthood by allele-specific, childhood trauma–dependent DNA demethylation in functional glucocorticoid response elements of *FKBP5*. This demethylation was linked to increased stress-dependent gene transcription followed by a long-term dysregulation of the stress hormone system and a global effect on the function of immune cells and brain areas associated with stress regulation. This identification of molecular mechanisms of genotype-directed long-term environmental reactivity will be useful for designing more effective treatment strategies for stress-related disorders.

Biology in Developmental Psychopathology

Conclusions

- Many questions remain about childhood and adolescent psychopathology
  - Are we on the right track in our current conceptualization and labeling of childhood and adolescent psychopathology?
- Adolescence is a key time period for the development of many forms of psychopathology seen in adulthood
  - Importance of brain developmental processes, hormonal changes, peer influences, societal/cultural norms and expectations, and the interaction of all these factors
- Understanding of the development of psychopathology will come through concurrent investigation across multiple levels of analysis
  - Genes, neurochemistry, morphology, brain volume and function, structural and functional connectivity, peripheral psychophysiology, behavior, interpersonal relations, environmental factors, cultural and societal/socioeconomic influences





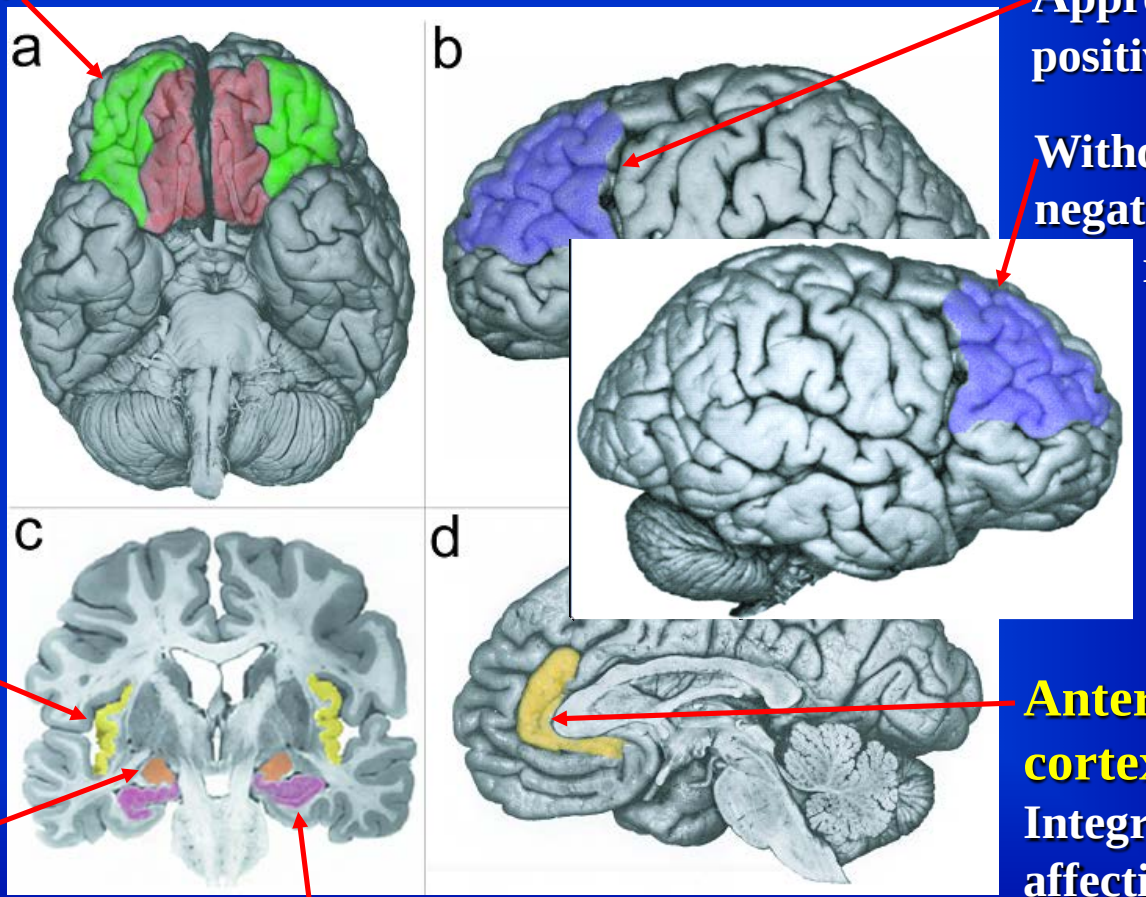
Buss et al. (2003) *Behavioral Neuroscience*

Key Brain Areas for Emotion

Orbitofrontal cortex:
Affective evaluation (decoding punishment and reward value)

Dorsolateral PFC:
Approach-related positive affect

Withdrawal-related negative affect; threat-related vigilance



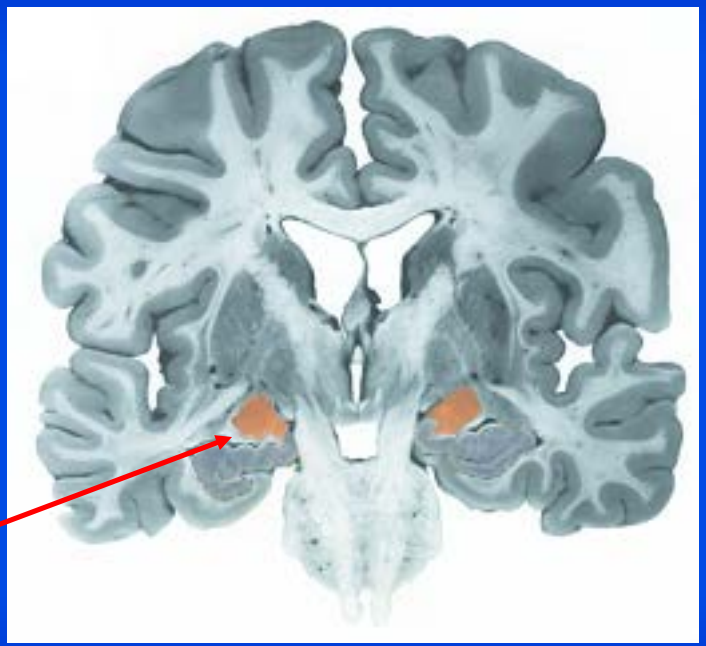
Insula:
Integration of sensory, affective, cognitive, and autonomic processing

Amygdala:
Vigilance for motivationally salient events; threat detection; emotional memory

Hippocampus:
Declarative memory; contextual fear

Anterior cingulate cortex:
Integration of sensory, affective, cognitive, and autonomic processing; conflict monitoring

Key Brain Areas for Emotion



Nucleus Accumbens:
Reward processing; positive emotion; salience detection

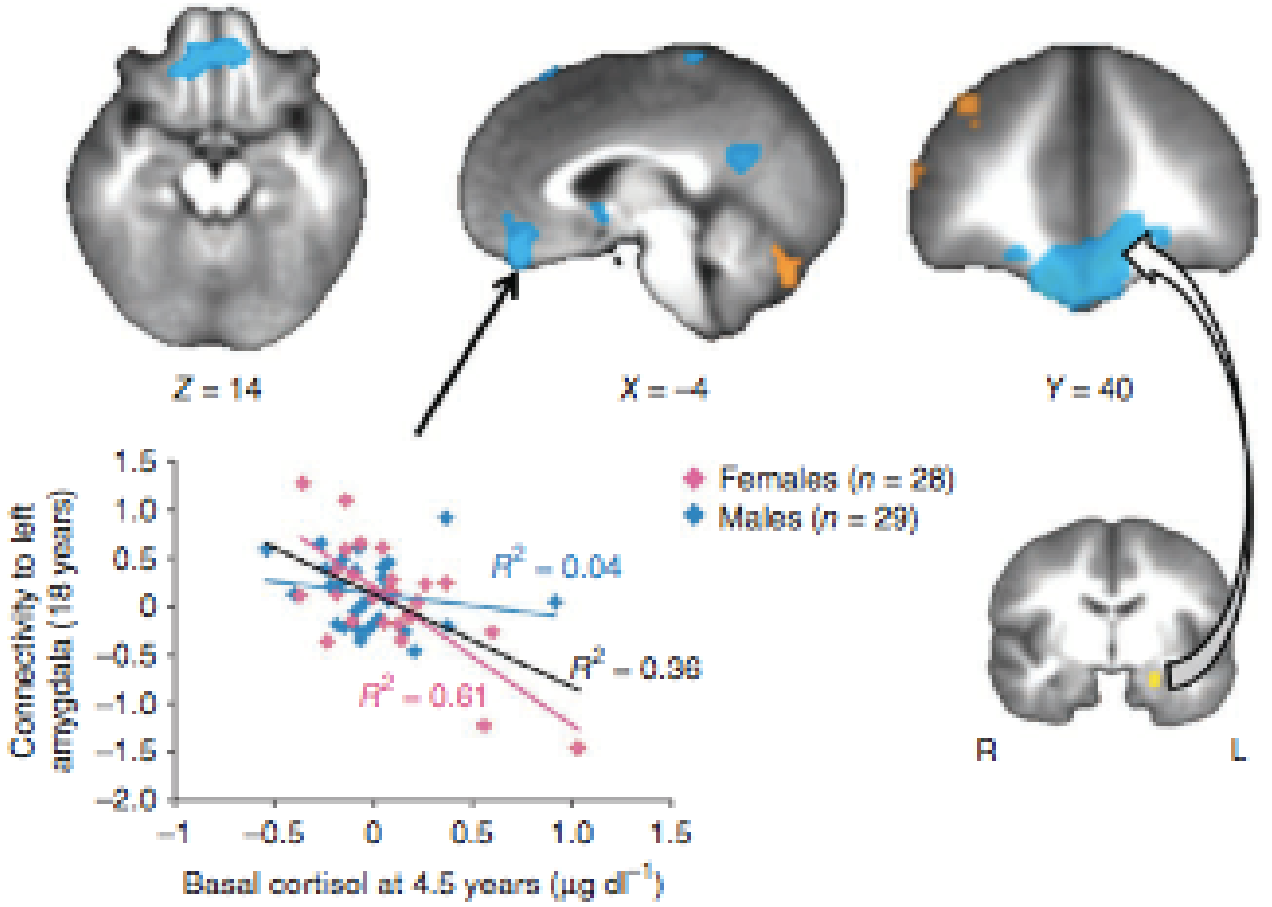


Figure 1 Correlation between late-afternoon cortisol at age 4.5 years and rs-FC to the left amygdala at 18 years. Connectivity between the left amygdala and vmPFC is significantly negatively associated with childhood cortisol (R^2 = 0.36, FDR-corrected P = 0.01). This effect is driven entirely by data for females (R^2 = 0.61, FDR-corrected P = 0.01).

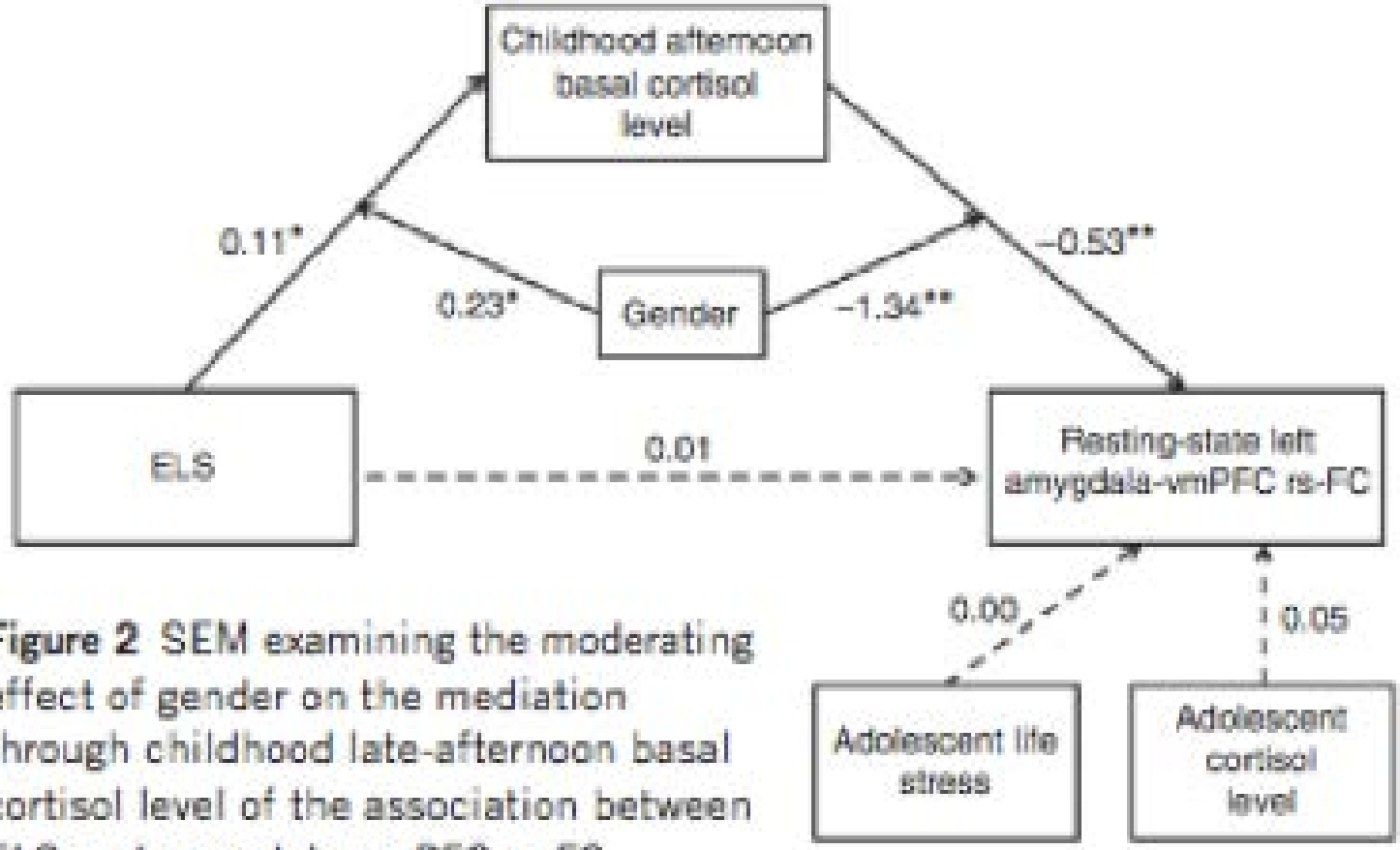


Figure 2 SEM examining the moderating effect of gender on the mediation through childhood late-afternoon basal cortisol level of the association between ELS and amygdala-vmPFC rs-FC.
The SEM demonstrated good fit: $\chi^2 = 1.89$, $P > 0.05$; root mean square error of approximation (RMSEA) = 0.00; standardized root mean square residual (SRMR) = 0.03; comparative fit index = 1.00. Paths are marked with unstandardized coefficients. $^*P < 0.05$, $^{**}P < 0.01$.

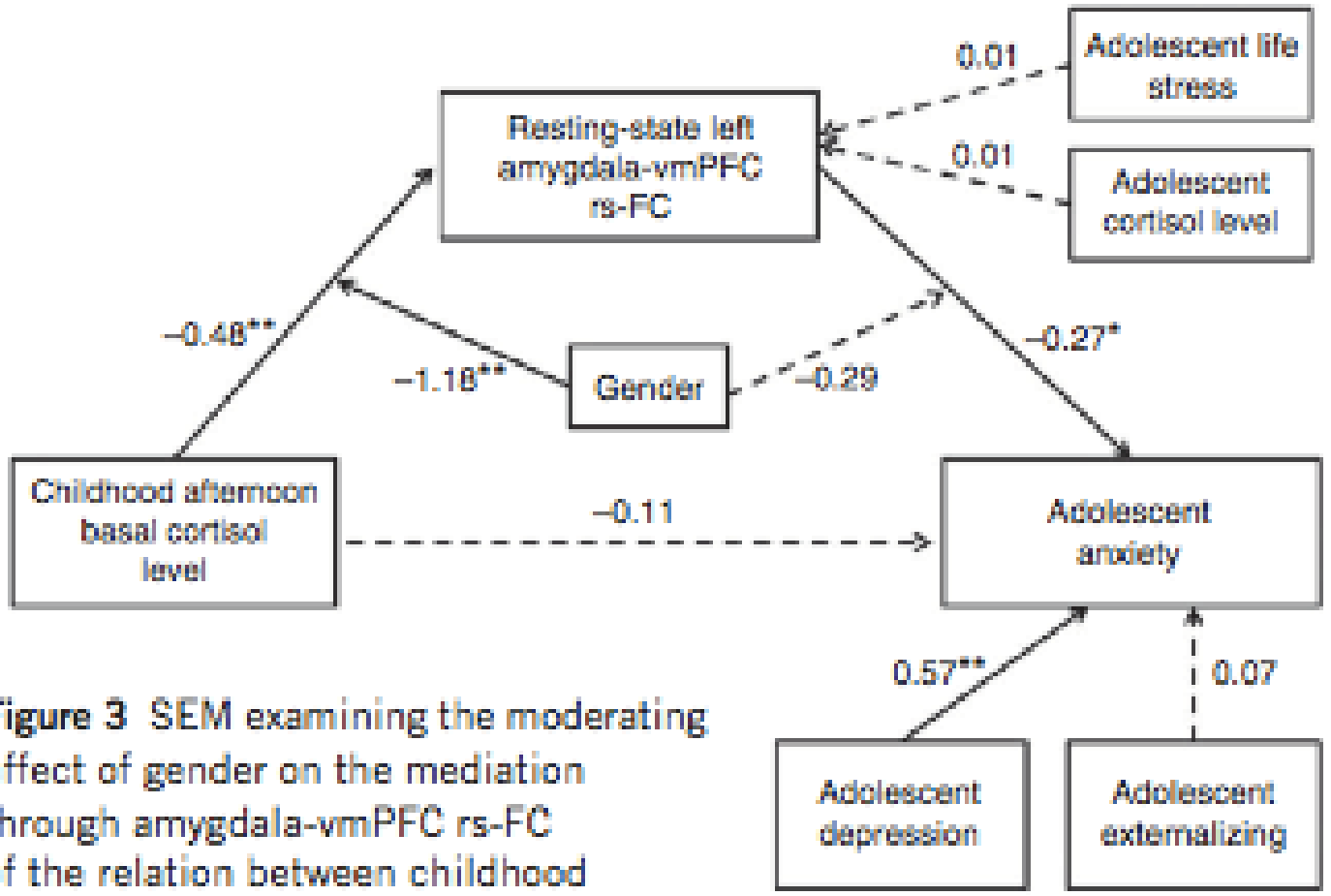


Figure 3 SEM examining the moderating effect of gender on the mediation through amygdala-vmPFC rs-FC of the relation between childhood late afternoon basal cortisol level and adolescent anxiety. The SEM demonstrated good fit: $\chi^2 = 9.95$, $P > 0.05$; root mean square error of approximation (RMSEA) = 0.11; standardized root mean square residual (SRMR) = 0.04; comparative fit index = 0.94. Paths are marked with unstandardized coefficients. $^*P < 0.05$, $^{**}P < 0.01$.