Models of Brain Development and Psychopathology

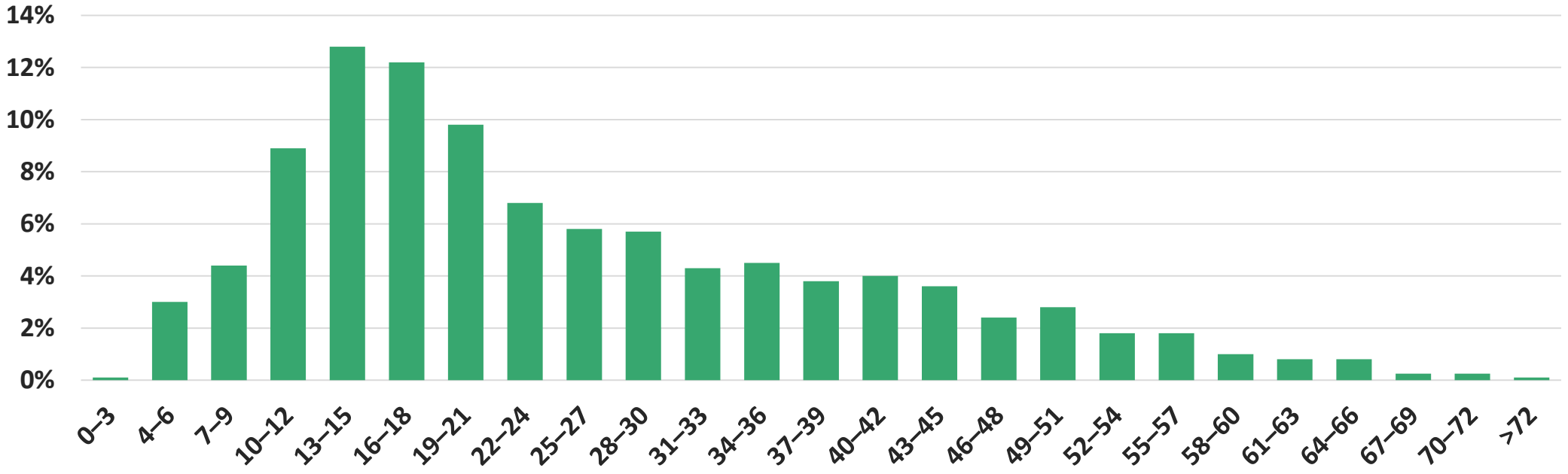
Adolescence: A Key Phase of Life for Health

Figure 4 | **Ranges of onset age for common psychiatric disorders.**

Paus, Keshavan & Giedd, 2008, *Nature Rev. Neuro.*

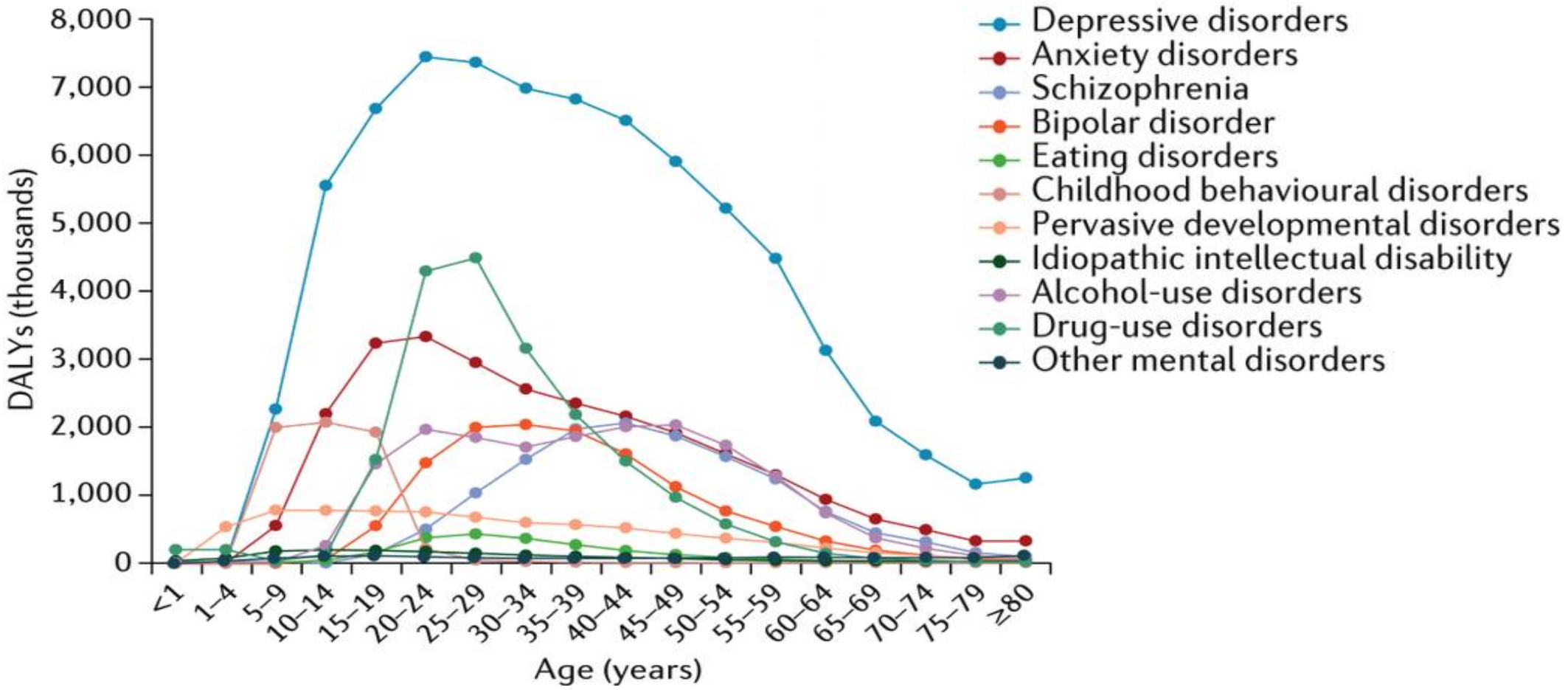
Adolescence: A Key Phase of Life for Health

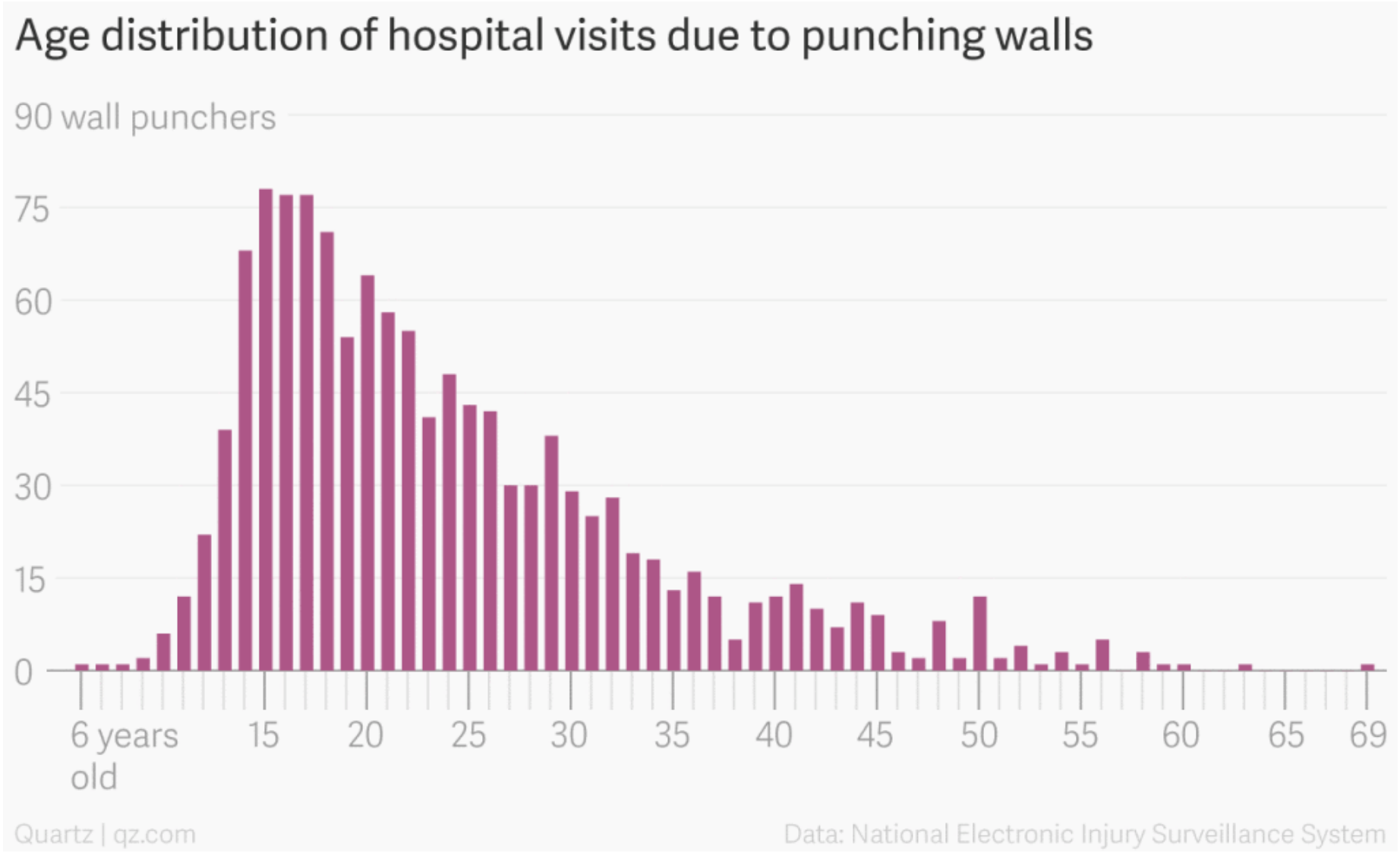
17%-22.6% of adolescents experience a depressive episode by age 18

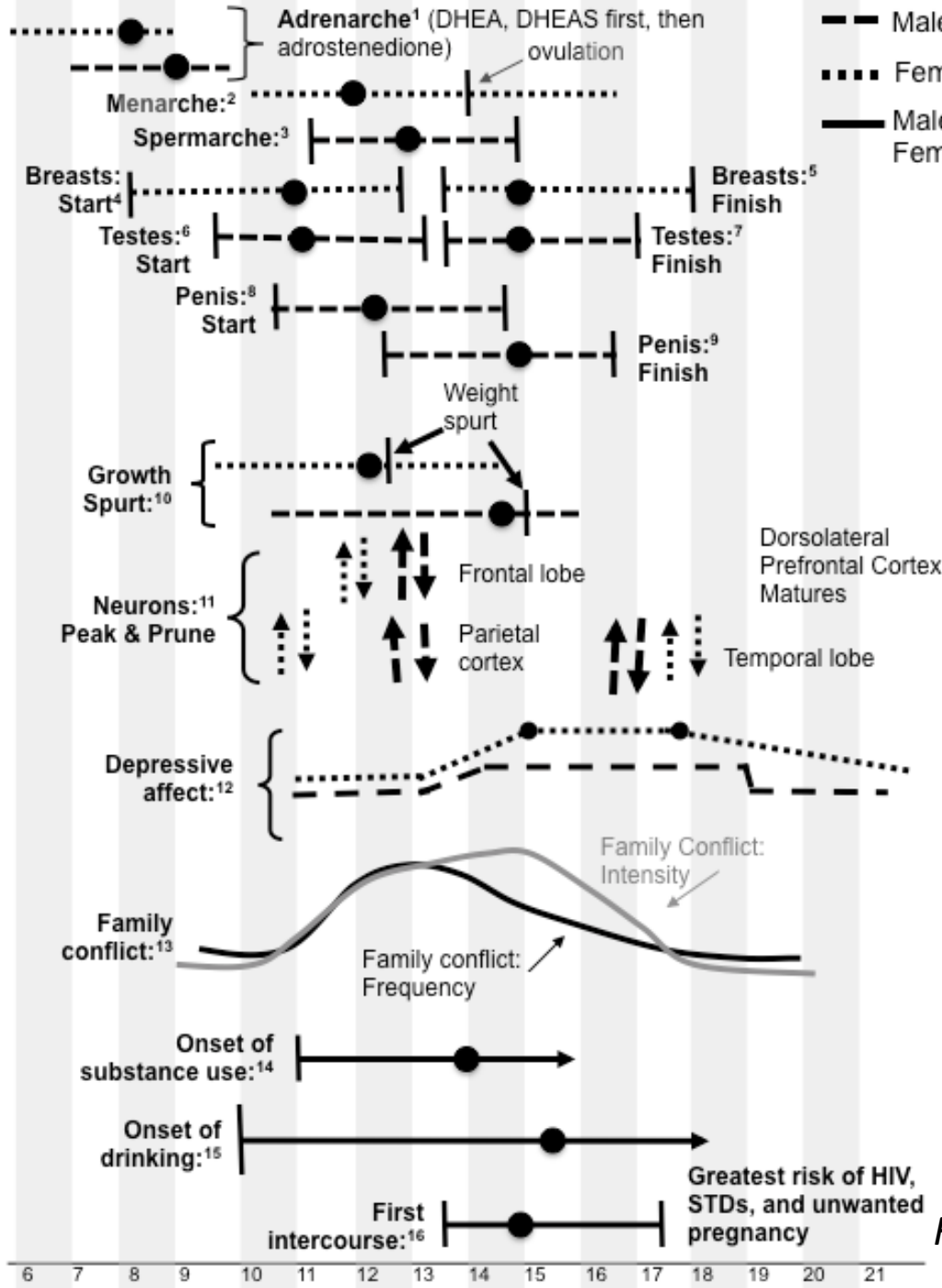


Zisook et al. 2007. Effect of Age at Onset on the Course of Major Depressive Disorder. Am J Psychiatry, 164:1539-1546

Adolescence: A Key Phase of Life for Health Across the Lifespan




Age distribution of hospital visits due to punching walls
90 wall punchers
75
60
45
30
15
0
6 years old
15
20
25
30
35
40
45
50
55
60
65
69
Quartz | qz.com
Data: National Electronic Injury Surveillance System



From Tom Hollenstein

Temporal relationships between brain development and adolescent mental Health

Cross-sectional association

Covariate (state)

Predictor

- Individual difference (intercept)
- Developmental process (slope)

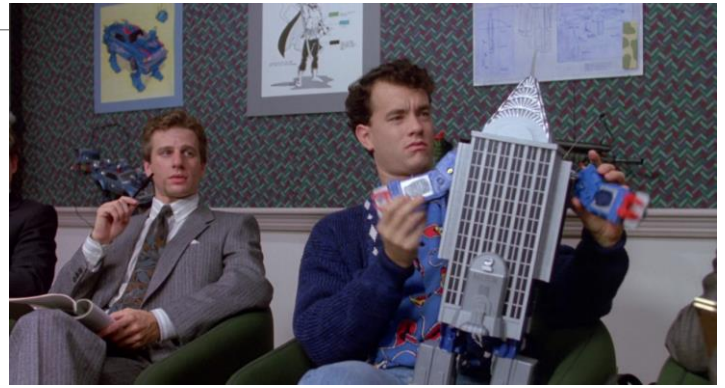
Scar

Development fast and slow

How does abnormal maturation confer risk?

Advanced maturation could be a risk or protective factor:

- Risk factor
  - Moving to a developmental phase before the previous one is complete (The "*Big*" effect)
  - One aspect of advanced development could place other aspects of on time development at risk (*Doogie Howser effect*)
- Protective factor
  - Advanced maturation could provide enhanced skills compared to peers (*Ferris Beuller effect*)



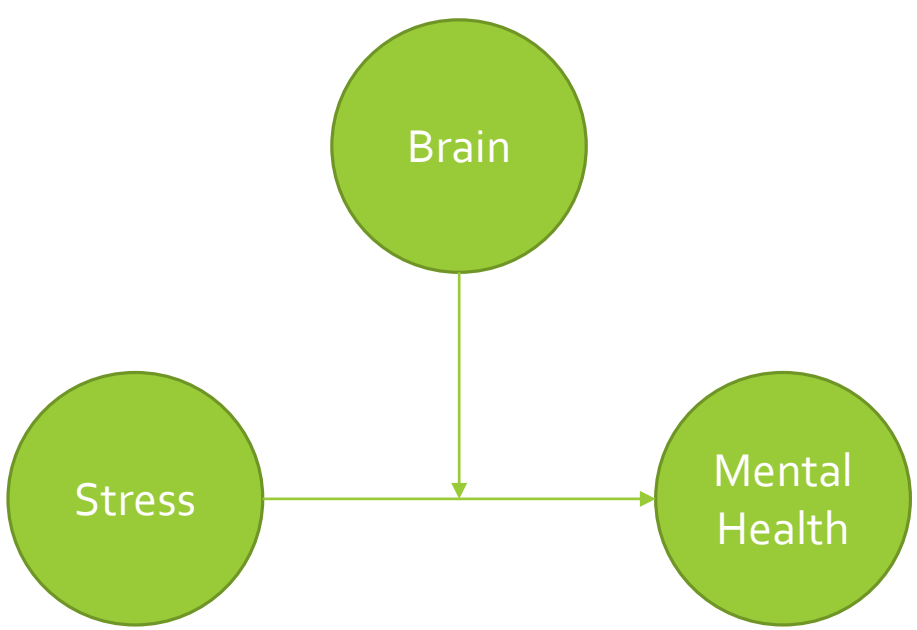
Development fast and slow

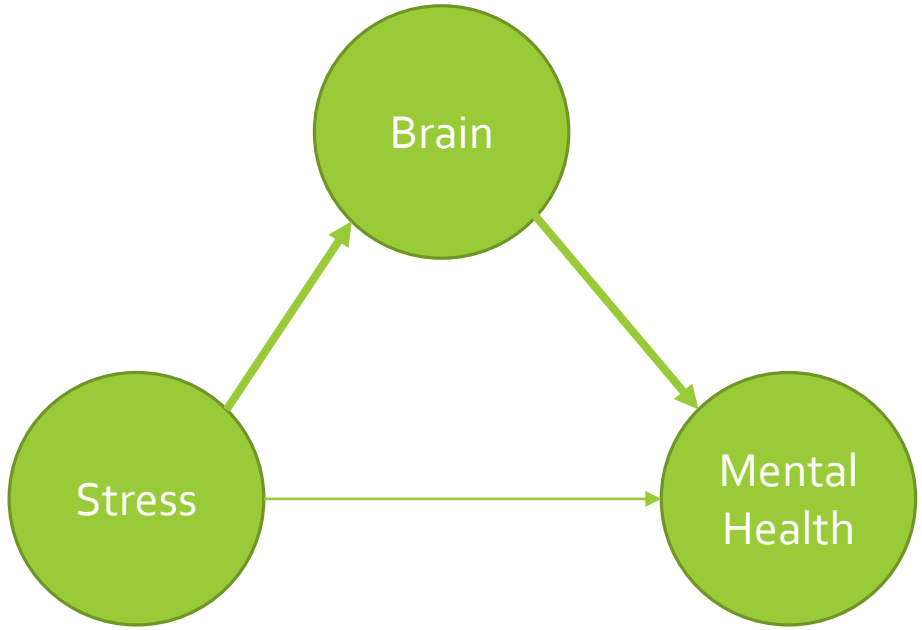
Delayed maturation could be a risk or protective factor:

- Risk factor
  - Poorer developmental capacities than peers (e.g., poorer self regulation) (Sean Penn Effect)
- Protective factor
  - Delayed entry into risky contexts (e.g., peer contexts) (Revenge of the Nerds)

Relationship between brain development and other risk factors (e.g., genetic, environmental)

Moderators versus mediators





To lump or split?

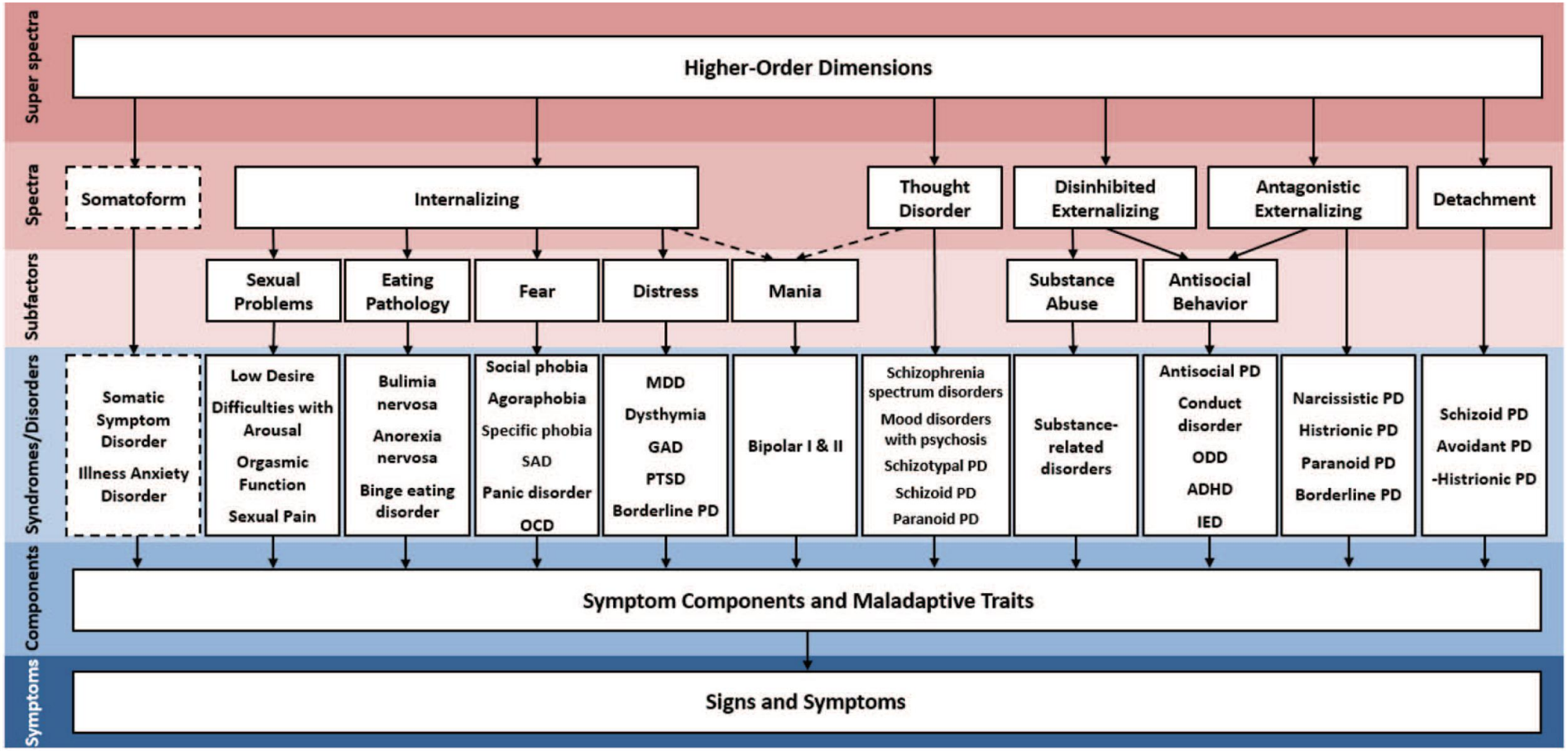


Figure 2. Spectra of the Hierarchical Taxonomy of Psychopathology. *Note:* Dashed lines indicate elements of the model that were included on provisional basis and require more study. Disorders with most prominent cross-loadings are listed in multiple places. Minus sign indicates negative association between histrionic personality and detachment spectrum. See the online article for the color version of this figure.

Kotov, Krueger, et al., 2017

Example of brain measures as a mediator

Amygdala Resting Connectivity Mediates Association Between Maternal Aggression and Adolescent Major Depression: A 7-Year Longitudinal Study

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Objective: The parent–adolescent relationship is an important predictor of adolescent mental health, especially depressive disorders. This relationship is constructed in the context of maturing emotion neurobiology and could help shape such neurobiology in ways that are important for current and future mental health. Amygdala resting-state functional networks have been linked to depression, but whether such resting connectivity is associated with parent affective behaviors or acts as a salient mediator between parenting and risk for depressive disorder is unknown.

Method: In the present study of 128 individuals, a 7-year longitudinal design was used to examine how observed maternal aggressive behavior during mother–adolescent interactions in early adolescence (12 years) predicted amygdala (whole and subregion)-based resting connectivity in mid adolescence (16 years). In 101 of those participants, whether altered amygdala resting-state connectivity mediated the association between maternal aggressive behavior and the first onset of major depressive disorder (MDD) in late adolescence (19 years) was analyzed.

Results: Maternal aggression was related to resting-state functional connectivity between the amygdala and right superior temporal-posterior insula-Heschl gyri, bilateral visual cortex, and left temporal and insula cortices (the latter being driven by the centromedial amygdala subregion; $p < .001$). Further, amygdala and centromedial amygdala connectivity with the temporal and insula cortices mediated the association between maternal aggression and late adolescent-onset MDD (CI 0.20 to 2.87; CI 0.13 to 2.40, respectively).

Conclusion: These findings are consistent with previous literature documenting the importance of amygdala resting networks for adolescent depression but further suggest the importance of parental affective (particularly aggressive) behavior in the development of such functional connectivity patterns during this period of peak onset for mental health disorders.

Key words: amygdala, resting state functional connectivity, adolescent, maternal aggression, parent–adolescent relationship

J Am Acad Child Adolesc Psychiatry 2017;56(11):983–991.

The transition from childhood to adolescence represents a significant shift in the role of parents, whereby adolescent autonomy and peer influences need to be renegotiated, often resulting in parent–adolescent conflict.[1,2] The affective climate within the parent–adolescent relationship is a strong predictor of adolescent mental health. Specifically, parental expression of emotion and aversive parent–adolescent relationships are risk factors for adolescent depression and other mental illnesses.[3-5] Such parental emotion expression is a form of emotion socialization, which shapes the emotional climate within the family and influences the emotional development of children through processes such as modeling and social referencing. Parental expression of negative, angry, or aggressive emotions in particular has been associated with adolescent depression.[5-7] We previously found that maternal expression of aggressive behavior that is "out of context" (i.e., expressed during a positive interaction task) prospectively predicts the onset of adolescent major depressive disorder (MDD),[8] suggesting that such behavior can be particularly maladaptive.

Parental socialization of adolescent emotions occurs in the context of significant structural and functional changes taking place in the adolescent's brain[9-12] and could help to shape the maturation of developmentally plastic neural networks with consequences for emotion regulation (e.g.,[13,14]). In particular, the amygdala undergoes significant structural and functional development throughout adolescence, which is related to adolescent emotionality.[12-15] Importantly, recent evidence suggests that parental expression of negative emotion shapes a child's amygdala reactivity during affective processing.[16]

Amygdala resting-state functional brain networks also undergo significant developmental change[17] and are associated with affective processing[18,19] and depression in

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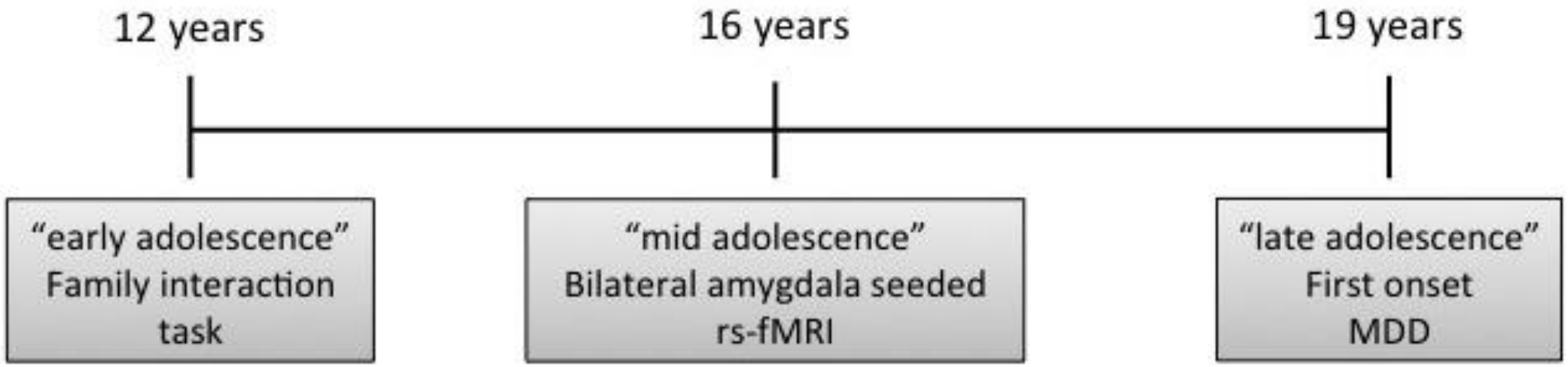
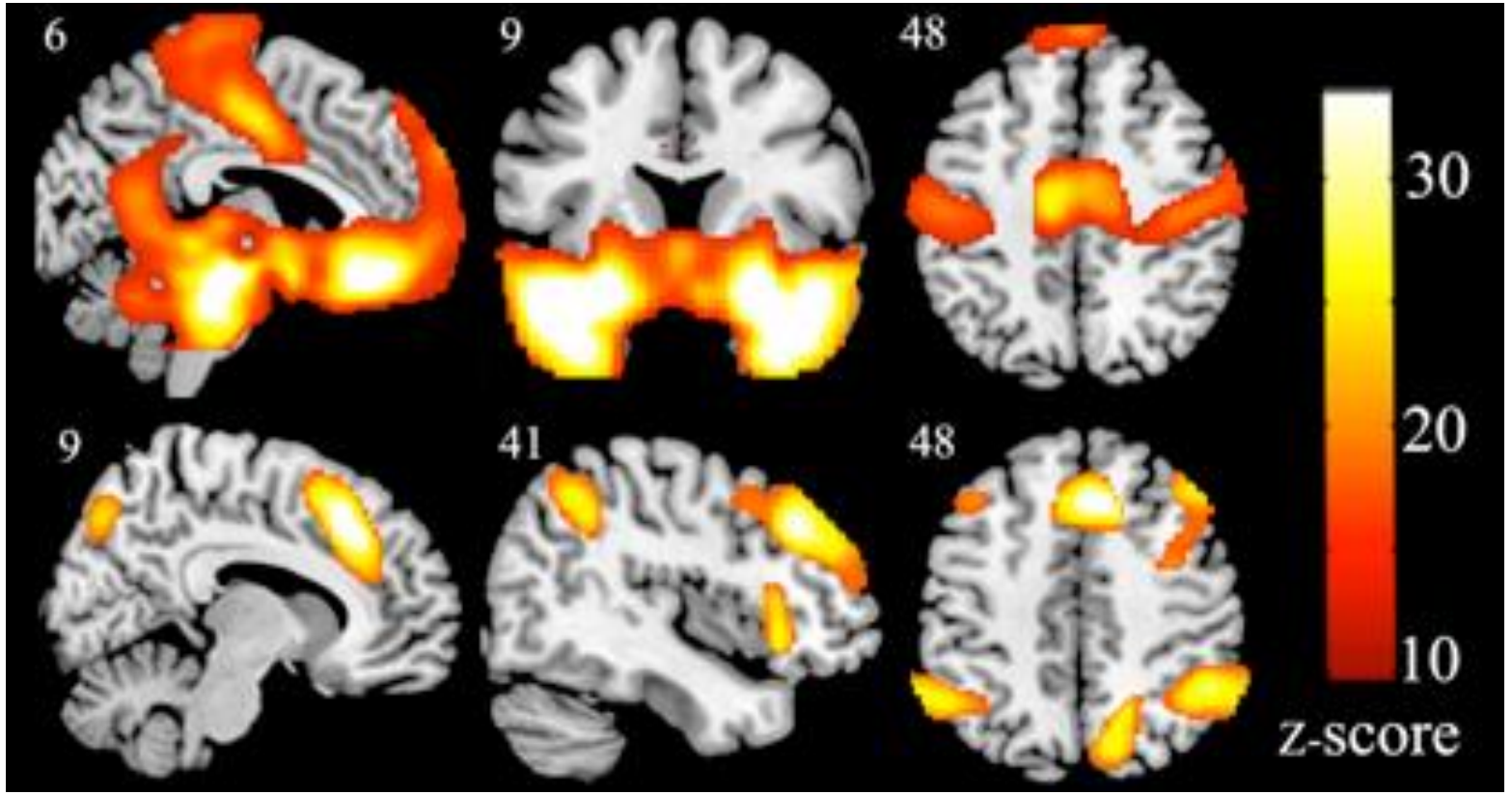
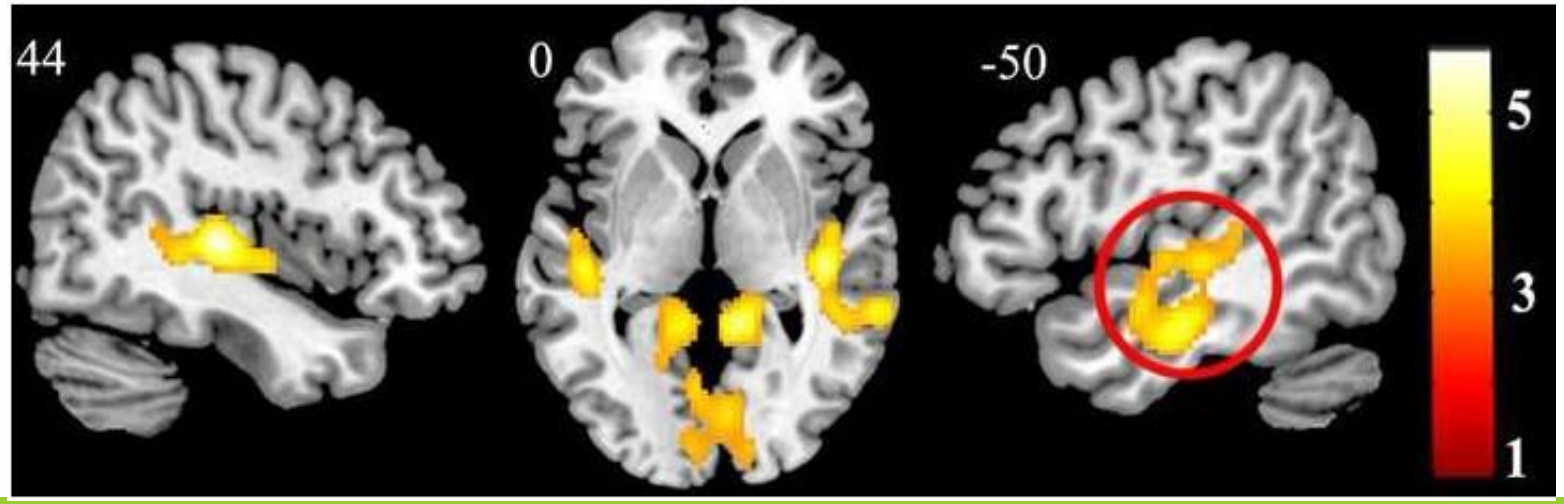

12 years
16 years
19 years
"early adolescence"
Family interaction
task
"mid adolescence"
Bilateral amygdala seeded
rs-fMRI
"late adolescence"
First onset
MDD

Significant clusters representing positive correlation (top row) and negative correlation (bottom row) with the whole amygdala seed

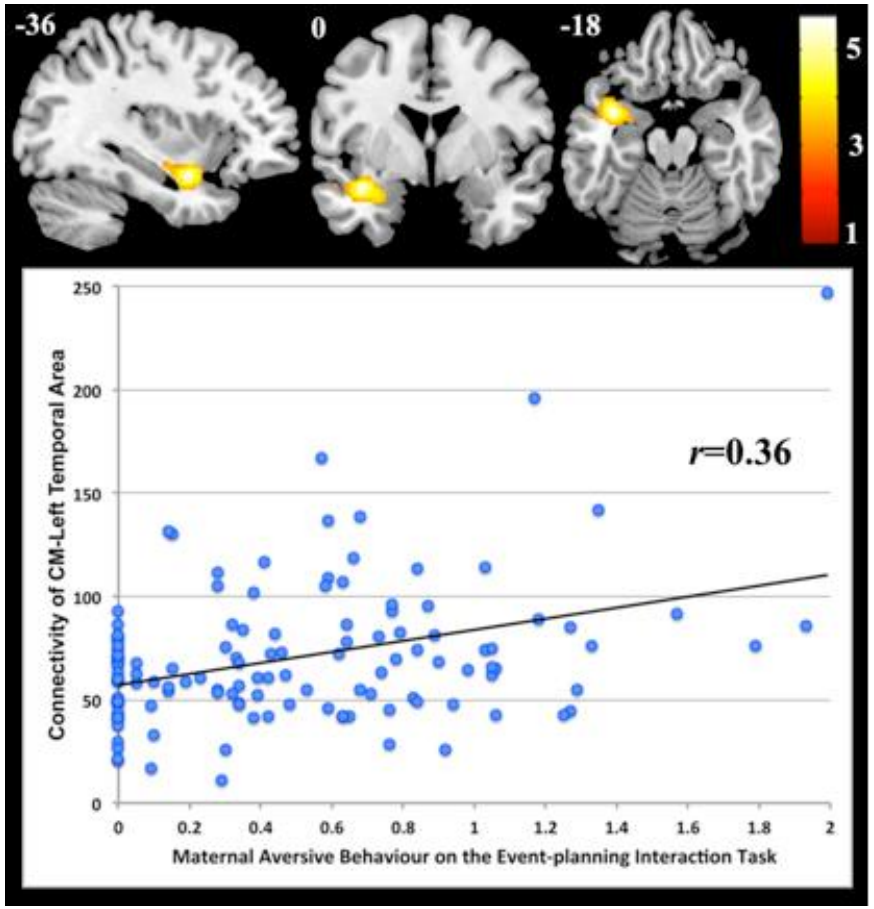


Association between amygdala connectivity and maternal aggressive behavior

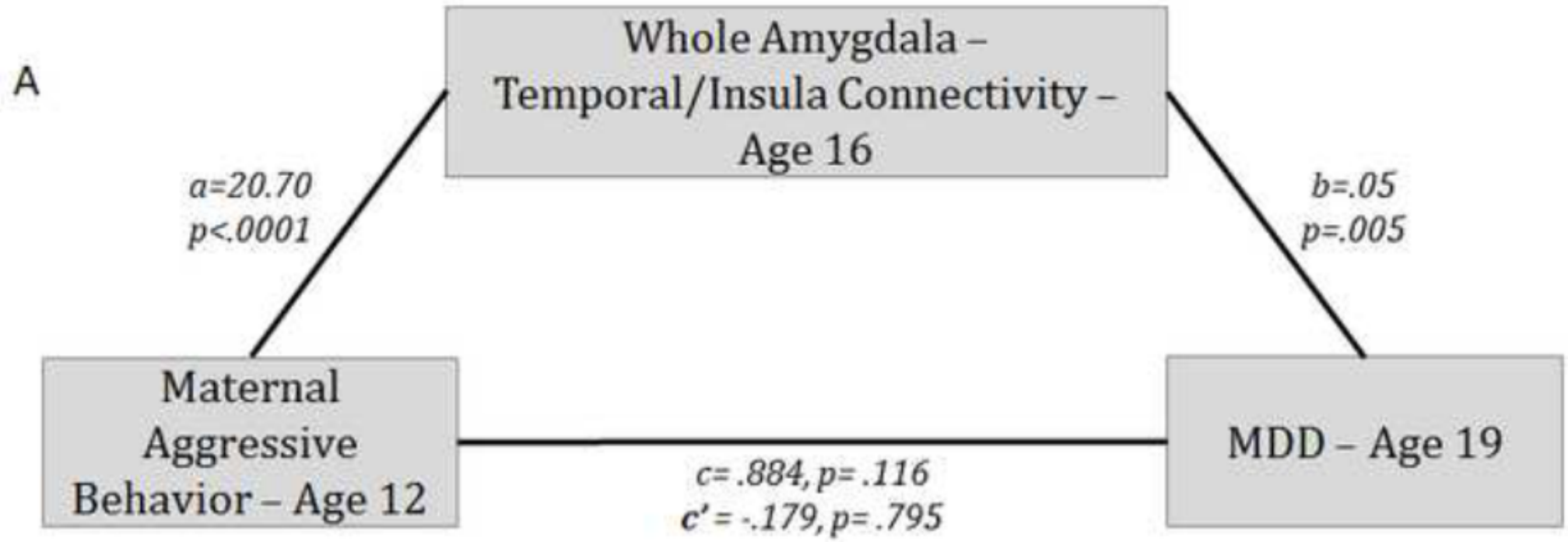
Cluster No.	Anatomical Region	Hemisphere	MNI Peak Coordinates (x,y,z)	Z-score	Voxels
1	Posterior insula, superior temporal and Heschl's gyri	Right	42,-26,4	5.07	909
2	Cerebellum and visual cortex	Bilateral	8,-44,-4	4.93	6983
3	Temporal/Insula cortex	Left	-38,2,-18	4.20	167



Association between CM amygdala connectivity and maternal aggressive behavior



Association between maternal aggression and adolescent onset MDD was mediated through whole amygdala-temporal/insula cortex connectivity



Association between maternal aggression and adolescent onset MDD was mediated through **CM amygdala-**temporal/insula cortex connectivity