Developmental Trajectories of Prefrontal – Nucleus Accumbens Subcircuits Support Cognitive and Affective Control Across Adolescence

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Background & Motivation

- Neurodevelopmental theories of adolescence[1,2] propose that improvements in cognitive control and the rise and fall of affective influences on adolescent behavior are supported by changes in dopaminergic mesocorticolimbic circuitry.[3,4,5]
- Interactions between the nucleus accumbens (NAcc) and prefrontal cortex (PFC) support motivation and cognition[6] and are altered across psychiatric disorders with adolescent onsets, including mood and substance use disorders.[7,8]
- Importantly, like functional specialization within the PFC (e.g., dorsolateral vs ventromedial)[11,12], the NAcc includes functionally distinct ***core*** and ***shell*** subdivisions that primarily support affective/motivational[14] and cognitive[13] processes, respectively.
- Studies have shown that the maturation of PFC-NAcc connectivity supports both affective/motivational[9] (e.g., sensation-seeking, reward/socioemotional sensitivity) and cognitive[10] (e.g., inhibitory control) development throughout adolescence; however, the relative contribution of NAcc ***core*** and ***shell*** to the developmental specialization of this circuitry remain unknown.
- Further, adolescent changes in dopaminergic function support the maturation of PFC-NAcc connectivity[9]; however, dopaminergic dynamics differ between the ***core*** and ***shell***, and the role of each subdivision in the developmental modulation of PFC connectivity remains unknown.[15]
- Human developmental studies using typical neuroimaging methods (e.g., at 3T) are limited in partitioning smaller structures, like the NAcc, into their constituent parts, obfuscating meaningful anatomical, physiological, and functional differences.

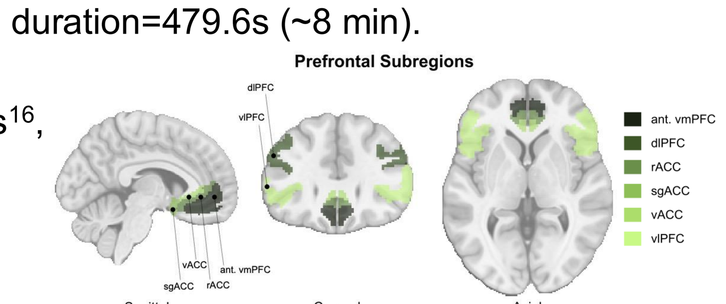
Here, we leveraged 7T neuroimaging to partition the NAcc into core and shell subdivisions. We characterized circuit-level maturational trajectories from adolescence into adulthood and examined the extent to which distinct pathways support the balance between affect-driven behaviors and cognitive control in adolescence into adulthood.

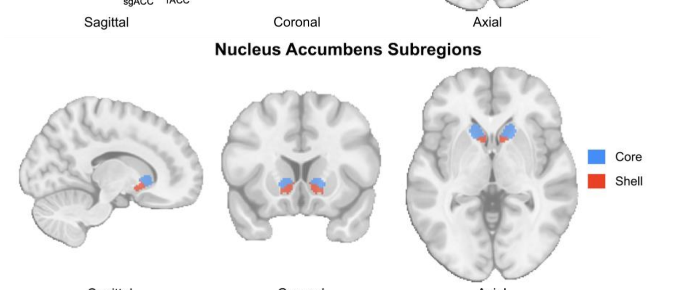
Hypotheses

- **NAcc core circuitry supporting cognitive-motor integration will exhibit age-related increases in functional coupling with executive control cortical structures (e.g., lateral PFC) and will support developmental improvements in cognition.**
- **NAcc shell circuitry supporting affective-motivational salience will exhibit age-related decreases in functional coupling with corticolimbic structures (e.g., ventral portions of ACC/PFC) and will support developmental decreases in affective sensitivity.**

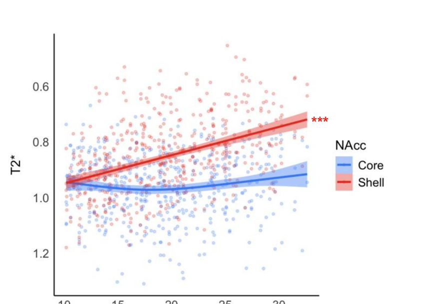
Study Design & Analyses

- **Participants:** Longitudinal 7T fMRI data from 176 healthy participants, ages 10-32 years, with up to 3 visits (274 total visits). T1w MRI: TR=6000, TE=2.47ms, voxel size=1x1x1mm, total duration=5m14s. T2* BOLD rsfMRI: TR=2.18, TE=23ms, voxel size=2x2x2mm, total duration=479.6s (~8 min).
- **Atlas-based region-of-interest (ROI) definitions:** medial PFC subregions were defined using Mackey & Petrides[16], dorsolateral PFC using Glasser[17], and ventrolateral PFC using Brainnetome[18]. NAcc core and shell subregions were defined using Tian[19].





- **Resting-state functional connectivity (RSFC):** time courses were extracted using the first PCA component within each ROI; Pearson correlation coefficients were computed between PFC and NAcc ROI pairs and normalized using Fisher's z transformation. Exploratory whole-brain analyses were performed for each NAcc subregion.
- **NAcc tissue iron:** T2* volumes were (z-score) normalized to whole brain mean, which were aggregated voxel-wise across all volumes resulting in one normalized image per participant.[20] nT2*w was extracted from NAcc core and shell subregions.

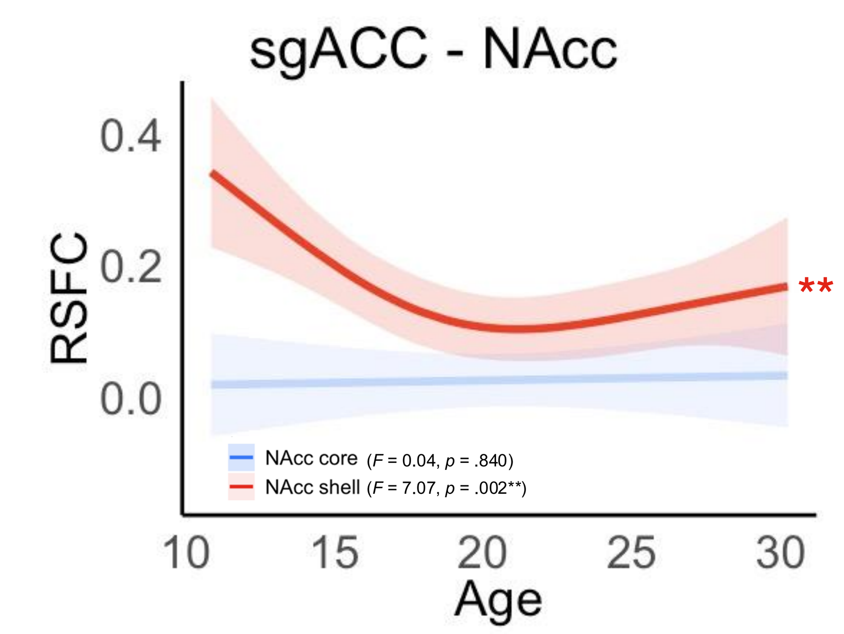


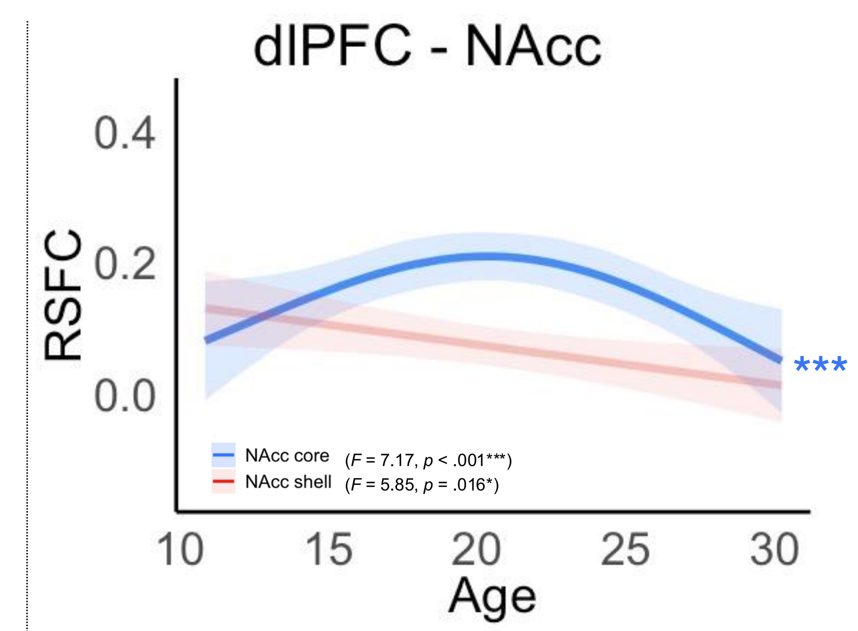
- **Behavioral Measures:** Affective measures included the Youth/Adult Self-Report (YSR[25]/ASR[26]), and cognitive measures included the antisaccade task.[27]
- **Psychological domain decoding[21]:** whole-brain voxel-wise RSFC maps were computed for NAcc core and shell; activation probability maps were obtained for terms present in Neurosynth[22] and the Cognitive Atlas.[23] Cortical regions were parcellated using Schaefer[24] and associations tests (z) quantified the extent to which cortical activations were consistently found in previous studies mentioning a given term.
- Generalized additive mixed models (GAMMs)[28] were used to characterize non-linear developmental trajectories. Behavioral associations were tested linearly while controlling for non-linear age effects.

Results

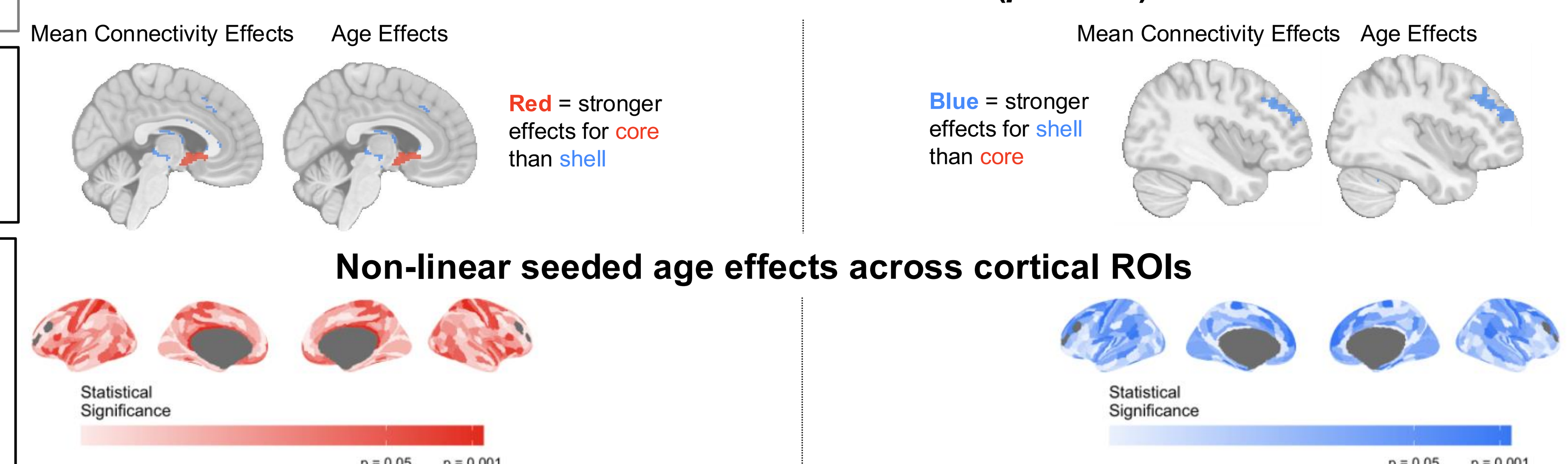
NAcc shell | ***NAcc core***

PFC-NAcc subcircuits have unique developmental trajectories by subdivision

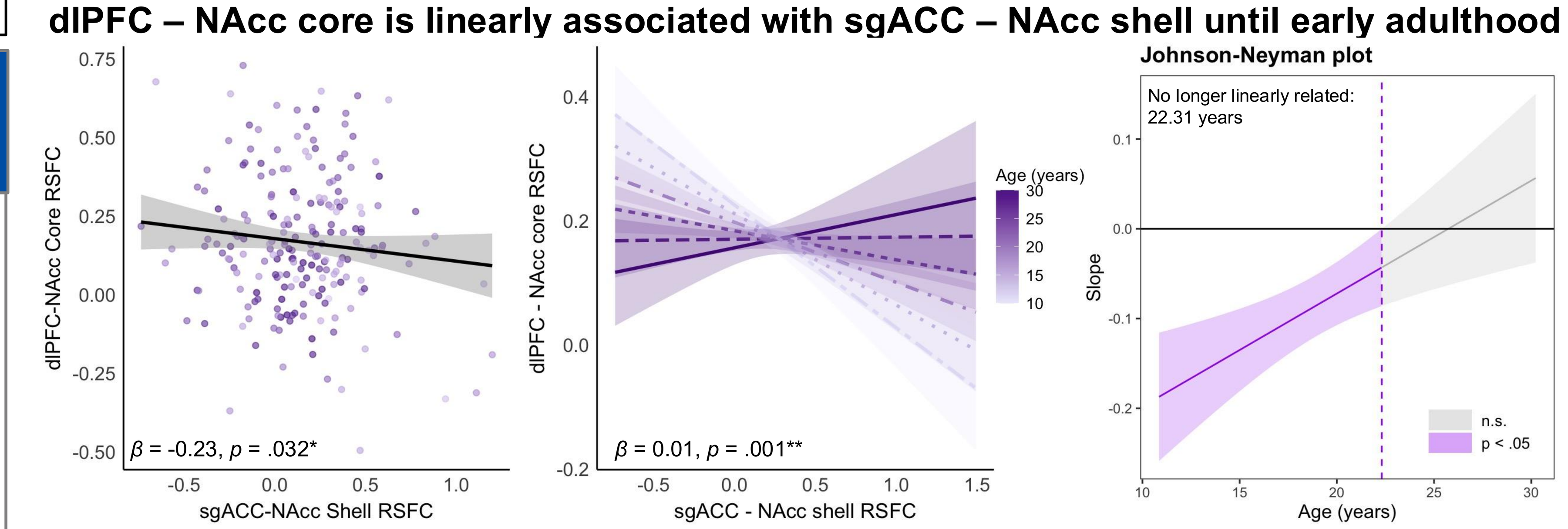




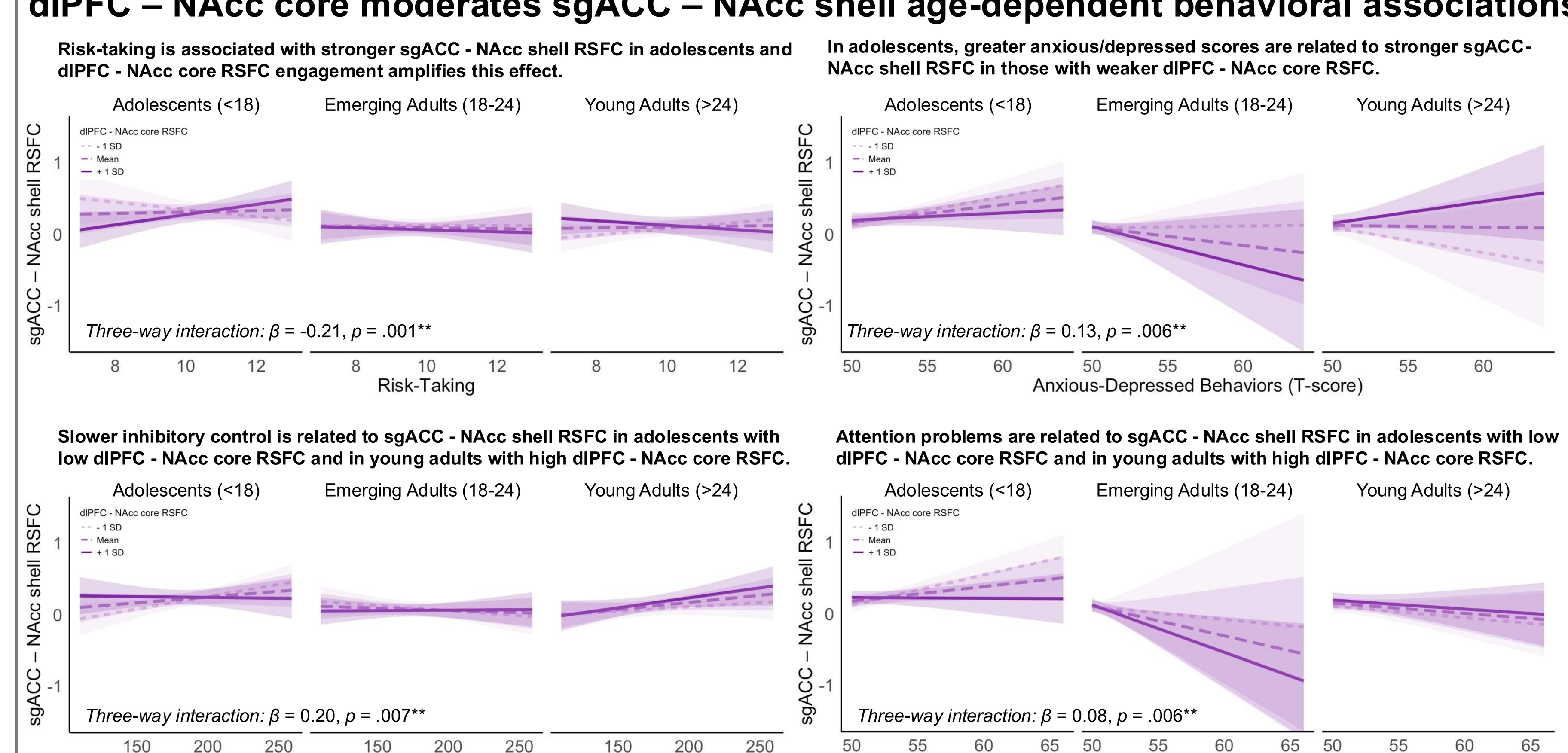
Seeded whole-brain RSFC reveals NAcc shell effects in sgACC and NAcc core effects in dlPFC (p = .001)



dlPFC – NAcc core is linearly associated with sgACC – NAcc shell until early adulthood

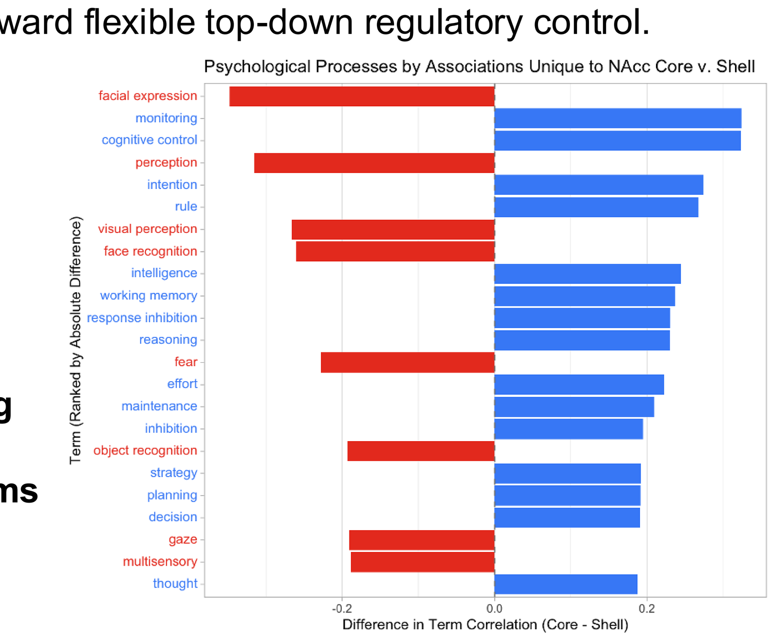


dlPFC – NAcc core moderates sgACC – NAcc shell age-dependent behavioral associations



Discussion

- Age-related effects of NAcc core and shell connectivity with the PFC were specific to the dlPFC and sgACC, replicating previous whole NAcc findings,[29] which may reflect a developmental trade-off in PFC signaling to NAcc, switching from affective sensitivity and reactivity predominantly biasing motivated behaviors to top-down executive control refinement facilitating goal-directed behaviors.
- As hypothesized, NAcc core circuitry was primarily associated with cognitive control whereas NAcc shell circuitry was mainly related to affective salience processing.
- dlPFC – NAcc core RSFC increased as sgACC – NAcc shell RSFC decreased before functionally decoupling around age 22, providing a circuit-level mechanism that may inform the timing of clinical interventions to improve treatment efficacy (e.g., TMS in trMDD).[30]
- Adolescents predominantly rely on fronto-striatal circuitry's ventral pathway (sgACC – NAcc shell) underlying affective processing while engagement of the dorsal pathway (dlPFC – NAcc core) is still immature and fails to sufficiently downregulate the ventral subcircuit.
- By early adulthood, stronger cognitive control networks relying on fronto-striatal circuitry's dorsal pathway can modulate affective processing in response to demands, suggesting maturation toward flexible top-down regulatory control.
- **Together, our findings suggest a fundamental reorganization of PFC-NAcc subcircuits during the transition from adolescence into adulthood that underlie declining affective influences (e.g., reward/ emotion-driven) and support cognitive refinement (e.g., working memory, inhibitory control), supporting the Driven Dual Systems model of adolescent neurodevelopment.**



Future Directions

- Characterizing NAcc subregional connectivity development in participants with greater psychiatric variability may inform etiology and interventions.
- It remains unclear how the NAcc subregions interface with other mesocorticolimbic nodes (e.g., amygdala subregions) throughout adolescent development to facilitate the transition into adulthood.
- Finally, given increased dopaminergic signaling to the NAcc in adolescence, ongoing work is examining the extent to which NAcc tissue iron supports circuitry maturation.

References

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