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

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Background & Motivation

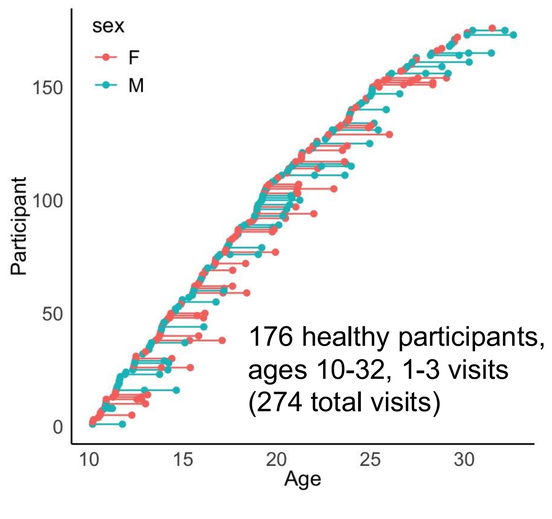
- Adolescence is characterized by cognitive improvements[1] but also increased risk for neuropsychiatric disorders.[2]
- Neurodevelopment of fronto-striatal circuitry, including functional interactions between the prefrontal cortex (PFC) and nucleus accumbens (NAcc), supports the development of cognitive control[3] and is altered in psychopathologies characterized by impairments in affective control (e.g., internalizing and externalizing disorders).[4,5]
- Both the PFC and NAcc are heterogeneous structures comprised of more dorsal and ventral subdivisions, broadly supporting cognitive and affective processing, respectively.[6,7]
- In a large longitudinal sample of 285 participants (763 total scans) healthy participants ages 8-35, we have previously shown PFC-NAcc age-related changes in functional connectivity to be specific to the dorsolateral PFC (dlPFC) and subgenual anterior cingulate cortex (sgACC),[8] which exhibited distinct maturational trajectories.
- Evidence from animal models indicates the dorsal NAcc ***core*** supports learning and invigorating behaviors and ventral ***shell*** supports hedonic processing and novelty-seeking; preliminary evidence in humans suggests distinct patterns of functional connectivity.[9,10]
- However, it remains unknown how the neurodevelopment of anatomically specific PFC-NAcc subcircuits mature to support cognitive and affective control in adolescence.

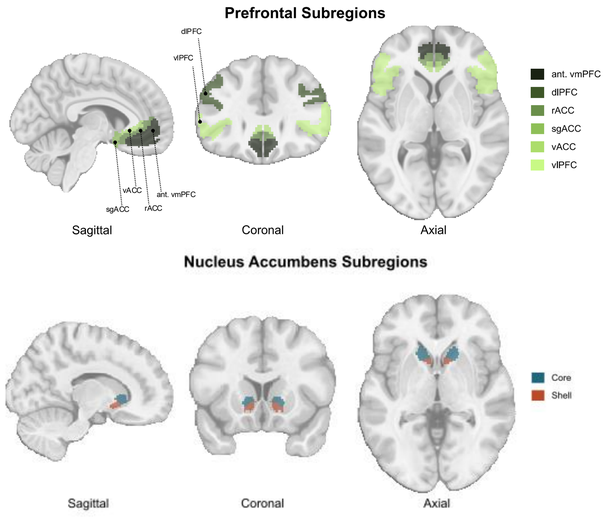
Hypothesis

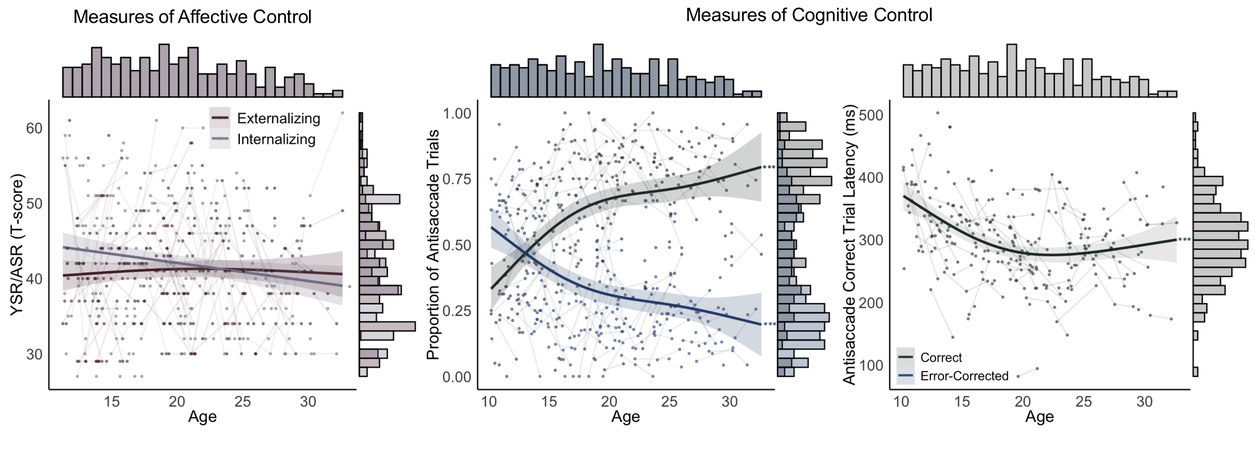
Age-related changes in PFC-NAcc functional connectivity will be specific to dlPFC – NAcc core and sgACC – NAcc shell, following cognitive/dorsal and affective/ventral pathways, each supporting these respective behaviors.

Study Design & Analyses

- **7 Tesla scan acquisition parameters:** 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:** PFC ROIs were defined using the Mackey & Petrides,[11] Glasser,[12] and Brainnetome[13] atlases, and NAcc ROIs using Tian.[14]
- **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.
- **Affective control measures:** self-reported internalizing and externalizing behaviors were determined using the Youth/Adult Self-Report (YSR[15]/ASR[16]).
- **Cognitive control measures:** inhibitory control was evaluated using the antisaccade task.[17] Behavioral measures of interest included percent of correct trials, percent of error-corrected trials, and latency on correct trials.
- ***Statistical analyses***
  - **Age-related change in PFC-NAcc RSFC:** We used big (generalized) additive (mixed) models (BAMs)[18] to characterize non-linear developmental trajectories and applied Bonferroni corrections for multiple comparisons.
  - **Brain-behavior relationships:** We tested three models to characterize relationships between age-related RSFC and measures of affective and cognitive control (all models controlled for non-linear age effects and Bonferroni corrections were applied to all tests):
    1. Linear associations between PFC-NAcc RSFC and behavior.
    2. Non-linear associations between PFC-NAcc RSFC and behavior.
    3. Age-moderated non-linear associations between PFC-NAcc RSFC and behavior.

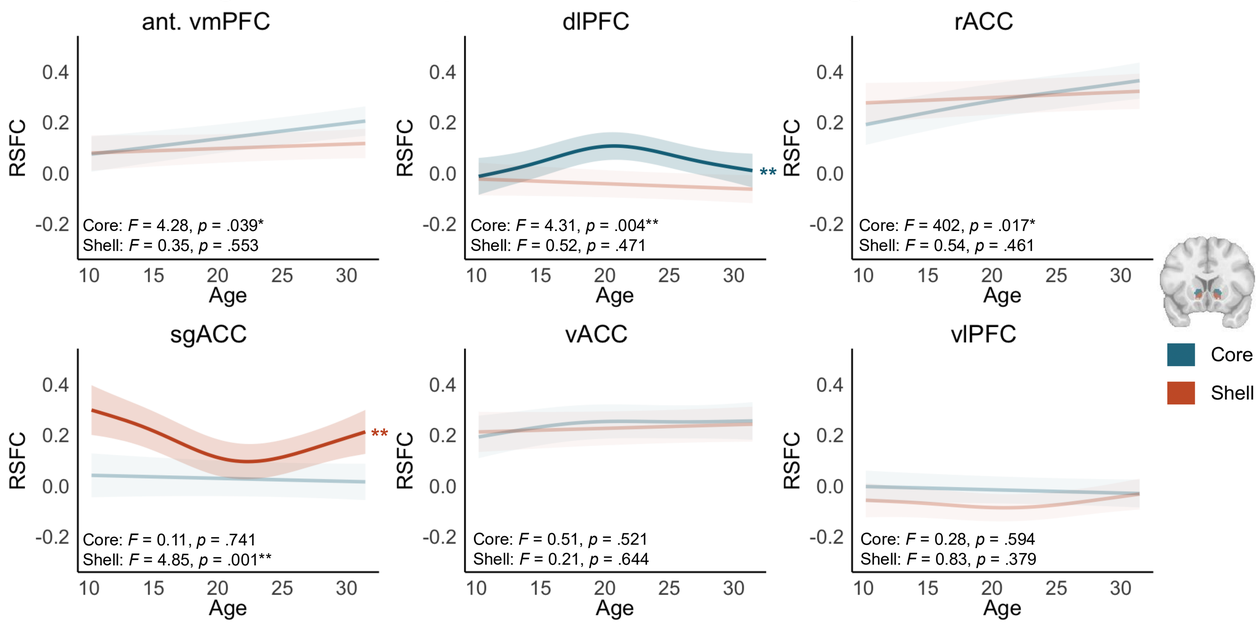




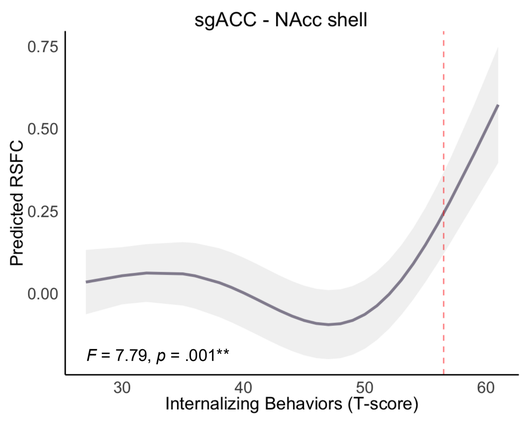


Results

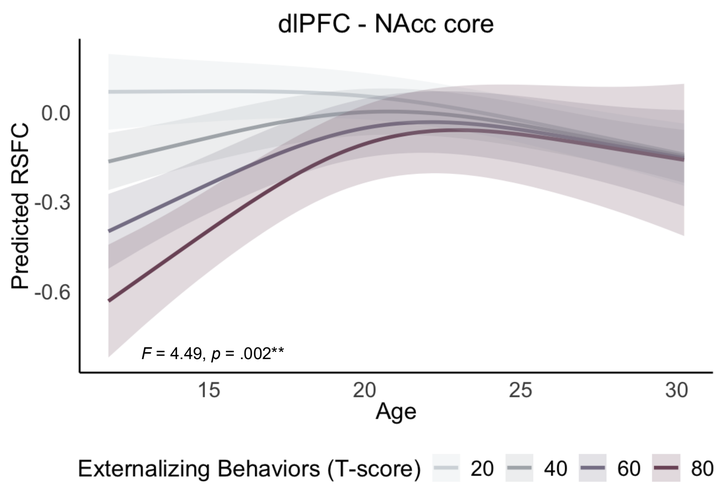
PFC-NAcc age effects are specific to dlPFC-core and sgACC-shell RSFC



Stronger sgACC – NAcc <u>shell</u> RSFC is related to higher internalizing



Weaker dlPFC – NAcc <u>core</u> RSFC is related to more externalizing at younger ages



Better inhibitory control is related to age-related decreases in dlPFC – NAcc core RSFC

Discussion

- As expected, age-related effects of NAcc core and shell connectivity with the PFC were specific to the dlPFC and sgACC, replicating previous whole NAcc findings but revealing greater neuroanatomical specificity.
- These findings may indicate a developmental shift in neural circuitry supporting motivated behaviors, with early adolescence characterized by stronger sgACC signaling to NAcc *shell* underlying heightened affective sensitivity but later adolescence and early adulthood by stronger dlPFC signaling to NAcc *core* underlying greater cognitive control.
- Brain-behavior associations supported a cognitive/dorsal and affective/ventral differentiation: particularly strong (ventral) sgACC – NAcc shell circuitry was associated with more internalizing; stronger (dorsal) dlPFC – NAcc core circuitry, especially in early adolescence, was associated with better inhibitory control and less externalizing.
- These findings elucidate how PFC-NAcc neurodevelopment may explain multiple phenotypes characterizing adolescence as a period of not only heightened affective sensitivity but also improved cognitive functioning by dissociating functions into anatomically specific subcircuits using ultra high-field longitudinal neuroimaging.
- Characterization of specific pathways undergoing protracted functional maturation linked with aspects of affective and cognitive control may provide a mechanistic neurobiological basis to identify potential therapeutic targets in transdiagnostic neuropsychiatric disorders with common adolescent onsets.

Future Directions

- The ventral tegmental area (VTA) in the midbrain sends dense dopaminergic projections to the NAcc,[7] connectivity that changes during adolescent development,[19] especially during motivated states; however, how VTA signaling to NAcc influences broader patterns of mesocorticolimbic circuitry maturation remains unknown.
- Finally, although preliminary evidence from animal models suggests distinct computational roles for dopamine in the NAcc core versus shell (related to reward prediction errors and incentive salience processing, respectively),[20] it remains unknown whether these differential dopaminergic functions are present in human adolescent neurodevelopment yet crucial to understanding typical maturation and characterizing alterations in dopamine-related psychopathologies.

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