Intrinsic Functional Connectivity of the Striatum in Developing Adolescents

Shady El Damaty (se394@georgetown.edu)
Center for Functional & Molecular Imaging (CFMI), Georgetown University Medical Center
3900 Reservoir Road NW Washington, D.C. 20007 USA
Goldie McQuaid, Kelly Martin,Valerie Darcey, Emma Rose, Diana Fishbein & John VanMeter

Abstract

The striatum is a system of nuclei within the basal ganglia hypothesized to integrate input from sensorimotor, limbic and executive cortical networks for context-sensitive action selection via recurrent striatal-thalamic-cortical projections. Classical anatomical studies have suggested a topographic organization of function in the striatum. However, the depth of detail of striatal functional topography and how it changes postpubertal development remains poorly understood. In this paper, we implement masked Independent Component Analysis (mICA) on resting state functional Magnetic Resonance Imaging (fMRI) collected from 135 youths (ages $11-14$) that had completed survey assessments of pubertal stage and predisposition for future risky behaviors. Split-half sampling revealed the fidelity of intrinsic striatal networks shared across youths plummets beyond estimates of 8 ICs. Striatal-cortical connectivity increased in a posterior-to-anterior gradient as a function of age and pubertal onset. Higher connectivity between the medial caudate and medial prefrontal cortex was present in more mature children (height threshold $p < 0.001$; cluster size $p_{FDR} < 0.05$) and inversely correlated with risk for future adverse outcomes ($p < 0.001$). Our results suggest delayed onset of refinement in connectivity between reinforcement learning brain areas predicts a proneness towards later risky behavior in adolescents. Overall, these methods demonstrate the utility of mICA and split-half sampling for reproducible functional parcellations of brain structures.

Keywords: striatum; resting state fMRI; unsupervised learning; blind source separation; adolescent development; reproducibility; subcortical parcellation

Introduction

Human cognitive maturity is exemplified by the ability to adaptively plan and execute sequences of goal-directed actions in the context of prior knowledge and a constant flow of competing sensory information. Youths on the road to maturity exhibit a heightened capacity for adapting behavior to external feedback, a skill known as reinforcement learning. Emotional salience of reinforcement signals can influence the emergence of this skill and consolidate risk-taking behaviors into habits that perpetuate through adulthood (van den Bos, Cohen, Kahnt, & Crone, 2011; Blair, Leibenluft, & Pine, 2014). In support of this view, the dual systems model of adolescent brain development suggests risk/reward-related neural activity increases in the striatum at pubertal onset, long before synaptic remodeling of prefrontal cortex is completed (Steinberg, 2010). In this work, we apply an *unsupervised clustering method* to identify subdivisions of the striatum within developing adolescents. Furthermore, we provide reproducibility estimates across increasing model order to identify appropriate levels of descriptive depth for the striatum in our sample. Lastly, we present age-related differences in the functional connectivity between identified striatal subdivisions and neocortex that are correlated with risk for adverse outcomes.

Methods

Subjects Youth participants were recruited from the Washington D.C. metro area for participation in the Adolescent Development Study - a prospective, longitudinal study with the aim of identifying the neurobehavioral antecedents and consequences of early alcohol use (Fishbein, Rose, Darcey, Belcher, & VanMeter, 2016). All youths ($N = 135$; 72 female, 63 male) recruited into the study had no history of neuropsychiatric disorders, recent head injuries or self-reported use of drugs or alcohol at baseline. Risk for future adverse outcomes (i.e., Substance use or mood disorders, delinquent behavior) was measured with the revised Drug Use Survey Inventory (DUSI-R). Developmental maturity was measured with the Pubertal Development Scale. All procedures were approved by the Georgetown University (GU) Institutional Review Board.

Data Acquisition Youths were scanned on a $3T$ Siemens Tim Trio system with a 12-channel head coil at the GU Medical Center. Whole-brain structural scans were acquired with a T1-weighted MPRAGE scanning sequence (TR/TE/TI=$1920/2.52/900ms$, $1x1x1.0mm^3$ voxel size). fMRI scans were collected while the subject was instructed to rest, keep their eyes open and allow their minds to wander (TR/TE$= 2280/30ms$, $3x3x3.0mm^3$ voxel size, 5:42 min).

Data Processing Standard temporal and spatial preprocessing of images was performed in CONN v17a using SPM12 for slice timing correction, realignment for head movement, coregistration of functional and structural scans, spatial normalization to MNI152 space and spatial smoothing of whole-brain functional images with a $8mm$ FWHM kernel (Whitfield-Gabrieli & Nieto-Castanon, 2012). Anatomical component-based noise correction was implemented to minimize the effect of spurious non-neuronal confounds on the measured resting state blood oxygen level dependent (BOLD) signal (Behzadi, Restom, Liau, & Liu, 2007). The BOLD signal was despiked with a hyperbolic tangent squashing function before denoising then bandpass filtered ($0.008 - 0.10Hz$).

mICA Intrinsic connectivity of the striatum was estimated with mICA using intensity and variance normalization, single-subject Singular-Value Decomposition (SVD), group-level Principle Component Analysis followed by fastICA for IC estimation and GICA1 for estimating subject-level factor loading maps. Left and right analysis masks were generated from a probabilistic atlas of the striatum ($p > 0.04$) and masked functionals were smoothed at $4mm$ FWHM (Keuken & Forstmann, 2015). Fifty-six components were retained for subject-level SVD dimensionality reduction based on Akaike's Information Criterion calculated with the GIFT toolbox v3.0a (Egolf, Kiehl, & Calhoun, 2004). Model orders reproducible across subjects were identified using split-half sampling with 500 repetitions across estimates ranging from 1 to 56 components. Split-half sampling estimates reproducibility by repeated random splitting of the subject pool into two groups, performing ICA over increasing model order then calculating the cross-correlation between the matched components of the two groups.

Results

Model Order Selection Local maxima of mean IC fidelity were identified at $1-4$ and 8 for left and right masks across subjects (Fig 1a). We selected 8 ICs to explore age-related intrinsic functional connectivity since ICs $1-4$ correspond to well-known anatomical subdivisions of the striatum. A striatal parcellation was generated by assigning each voxel a unique label corresponding to the maximum absolute factor loading value across all 8 components (Fig 1b).

Age Covariant Connectivity BOLD signals correlated between 304 $20mm^3$ cubes tiling the whole-brain and each of the 8 striatal ICs showed a posterior-to-anterior gradient in older youths ($p < 0.01$ *uncorr.*, Fig 1c). Functional segregation within the striatum was also observed. Anterior putamen was weakly coherent with higher visual cortex whereas medial caudate was more connected to medial prefrontal cortex (mPFC) in older subjects, suggesting a shift in brain development from sensory integration to refinement of reinforcement learning ($p < 0.001$, $p_{FDR} < 0.05$, Fig 1d).

Pubertal Maturity & Future Risk for Adverse Outcomes Physical changes due to pubertal onset also showed a posterior-to-anterior gradient in striatal-cortical connectivity ($p < 0.01$ *uncorr.*). Stronger mPFC and medial caudate connectivity was predicted by the pubertal development scale and lower risk for adverse outcomes measured with DUSI-R, suggesting that timed developmental changes in reinforcement learning brain regions is related to future risky behavior ($\beta_{risk} = -0.22$, $\beta_{puberty} = 0.04$, $p < 0.001$, $R^2 = 0.12$).

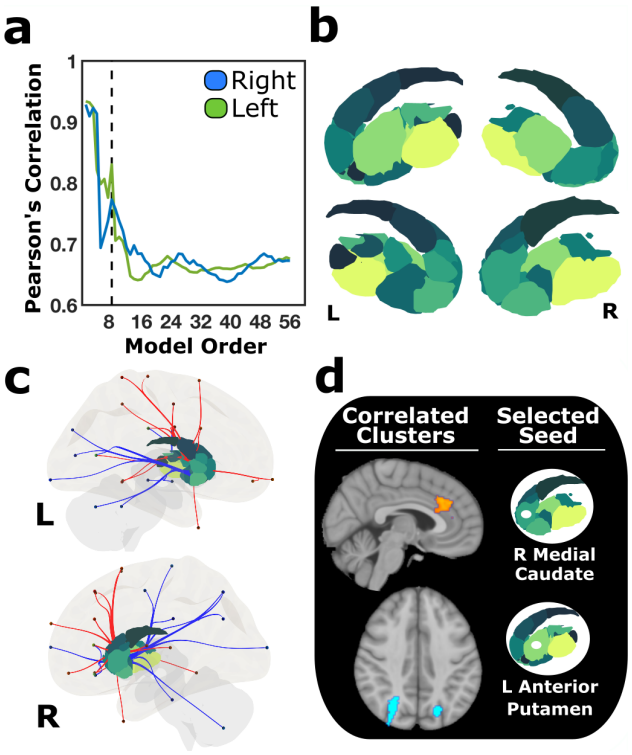

Figure 1: **a)** The striatum was found to be reliably broken down into $1-4$ or 8 networks across subjects. **b)** An 8 IC parcellation illustrated intrinsic functional connectivity nested within classical anatomical divisions of the striatum. **c)** Striatal subdivisions were more strongly correlated (*red lines*) with anterior regions and less coherent (*blue lines*) with posterior areas in older youths. **d)** Seed-to-voxel examples of age-related functional segregation within striatum corroborate posterior-anterior differences in connectivity.

References

Behzadi, Y., Restom, K., Liau, J., & Liu, T. (2007). A component based noise correction method (compcor) for bold and perfusion based fmri. *Neuroimage*, *37*, 90–101.

Blair, J. R., Leibenluft, M., & Pine, D. (2014). Conduct disorder and callous-unemotional traits in youth. *New England Journal of Medicine*, *371*, 2207-2216.

Egolf, E., Kiehl, K., & Calhoun, V. (2004). Group ICA of fMRI toolbox (GIFT). In *Proceedings of the organization of human brain mapping.*

Fishbein, D., Rose, E., Darcey, V., Belcher, A., & VanMeter, J. (2016). Neurodevelopmental precursors and consequences of substance use during adolescence: Promises and pitfalls of longitudinal neuroimaging strategies. *Frontiers in Human Neuroscience*, *10*, 296.

Keuken, M., & Forstmann, B. (2015). A probabilistic atlas of the basal ganglia using 7 t MRI. *Data in Brief*, *4*, 577-582.

Steinberg, L. (2010). A dual systems model of adolescent risktaking. *Dev Psychobiol*, *52*, 216-224.

van den Bos, W., Cohen, M. X., Kahnt, T. K., & Crone, E. (2011). Striatum-medial prefrontal cortex connectivity predicts developmental changes in reinforcement learning. *Cerebral Cortex*, *22*, 1247-1255.

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain connectivity*, *2*, 125.