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Archival Report

Age-Normative Pathways of Striatal Connectivity Related to Clinical Symptoms in the General Population

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ABSTRACT

BACKGROUND: Altered striatal development contributes to core deficits in motor and inhibitory control, impulsivity, and inattention associated with attention-deficit/hyperactivity disorder and may likewise play a role in deficient reward processing and emotion regulation in psychosis and depression. The maturation of striatal connectivity has not been well characterized, particularly as it relates to clinical symptomatology.

METHODS: Resting-state functional connectivity with striatal subdivisions was examined for 926 participants (8–22 years of age, 44% male) from the general population who had participated in two large cross-sectional studies. Developing circuits were identified and growth charting of age-related connections was performed to obtain individual scores reflecting relative neurodevelopmental attainment. Associations of clinical symptom scales (attention-deficit/hyperactivity disorder, psychosis, depression, and general psychopathology) with the resulting striatal connectivity age-deviation scores were then tested using elastic net regression.

RESULTS: Linear and nonlinear developmental patterns occurred across 231 striatal age-related connections. Both unique and overlapping striatal age-related connections were associated with the four symptom domains. Attention-deficit/hyperactivity disorder severity was related to age-advanced connectivity across several insula subregions, but to age-delayed connectivity with the nearby inferior frontal gyrus. Psychosis was associated with advanced connectivity with the medial prefrontal cortex and superior temporal gyrus, while aberrant limbic connectivity predicted depression. The dorsal posterior insula, a region involved in pain processing, emerged as a strong contributor to general psychopathology as well as to each individual symptom domain.

CONCLUSIONS: Developmental striatal pathophysiology in the general population is consistent with dysfunctional circuitry commonly found in clinical populations. Atypical age-normative connectivity may thereby reflect aberrant neurodevelopmental processes that contribute to clinical risk.

Keywords: ADHD, Depression, Development, General psychopathology, Psychosis, Striatum

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Corticostriatal and cortico-striatal-cerebellar circuits underlie diverse cognitive functions such as cognitive control, motor control and inhibition, reward prediction and processing, and emotion regulation (1–7). It is unsurprising, then, that striatal maturation plays a critical role in several neurodevelopmental and psychiatric disorders (8). A number of risk factors influence striatal development and increase susceptibility to mental health disorders (9–12). The understanding of healthy striatal maturation is therefore important for identifying developmental biomarkers of psychopathology and for distinguishing such biomarkers of individual clinical domains.

Recent resting-state functional magnetic resonance imaging (MRI) studies examining the development of striatal connectivity in the general population have used either small samples, with limited representation across developmental stages, or categorical samples (e.g., childhood, adolescence, young adulthood), rather than looking continuously across the age range (13–15). Prefrontal maturation lags behind that of the striatum, a discrepancy that contributes to increased behavioral dysregulation during adolescence and thus may increase risk for several neuropsychiatric disorders (16,17). Therefore, there is need for improved characterization of nonlinear changes in normative development of corticostriatal connectivity.

Striatal dysfunction is implicated in core deficits in attention-deficit/hyperactivity disorder (ADHD) including inattention, hyperactivity, and impulsivity (12,18,19). This neurodevelopmental disorder is characterized by developmental delays across the brain in both structure and function (20,21). Structural MRI studies find that children with ADHD have developmental trajectories lagging behind those of typically

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developing children by 1 to 3 years (20,22–24). Moreover, task and resting-state functional MRI studies have found delayed functional development in several cortical networks (21,25,26). While striatal dysfunction in ADHD has been widely reported (27–29), there is a dearth of research examining the development of striatal connectivity associated with ADHD.

Striatal development likewise plays a critical role in the neurodevelopment of psychosis and depression. For psychosis, the age of onset is later than in ADHD (i.e., adolescence or young adulthood); however, there is much evidence that genetic and environmental factors influencing striatal maturation alter dopamine levels and predispose toward psychosis (10,30). Importantly, aberrant striatal connectivity has been observed during the psychosis prodrome (31,32), as well as the first episode of psychotic illness (33,34), suggesting that these abnormalities reflect disease etiology and are not merely the result of treatment or long-term illness processes. Understanding the development of altered striatal connectivity may also provide insight into treatment of psychotic disorders, insofar as normalization of corticostriatal connectivity has been shown to predict response to antipsychotic treatment (35–37).

The incidence of depressive episodes increases in adolescence, which is likely the outcome of neurodevelopmental events increasing susceptibility (11,38). As with psychosis, studies of patients in the earliest phases of illness, before exposure to medication, suggest a role for altered striatal connectivity in the etiopathogenesis of depression (39,40). Reduced pregenual cingulate–striatal connectivity predicts greater subclinical depression severity (41). Further, general reductions in left caudate connectivity have been associated with subclinical depression (42). Thus, striatal circuits may be an early biomarker and key treatment target for depression.

While atypical striatal maturation is a likely contributor to the pathophysiology of multiple disorders, it is not clear whether this reflects unique disorder-specific neurodevelopmental pathways or a common pathway indicative of general psychopathology. Recent interest in the "p" factor, a single dimension that explains symptom severity across disorders, stems from findings that there is high comorbidity between disorders and that familial and individual lifetime psychiatric histories commonly cross clinical domains (43,44). Severity of general psychopathology is related to striatal dysfunction during reward processing in adults (45) as well as to resting-state striatal connectivity with the anterior cingulate cortex (ACC) in a developmental population (46). Therefore, it is unclear whether the maturation of particular striatal connections is related to particular symptom domains or to severity of psychopathology more generally.

Several recent studies have used growth charting to characterize age-normative brain development and determine whether clinical or cognitive traits are related to delayed or precocious connectivity (47–49). The current study followed a series of steps to identify the neurodevelopment of striatal connectivity in the general population and to examine the role of age-inappropriate connectivity in clinical symptom domains. First, we examined the development of resting-state functional connectivity with striatal subdivisions (1) in the general population using large, cross-sectional developmental datasets. Next, growth charting of age-related connections (ARCs) was performed to obtain individual scores reflecting age-normative connectivity. Associations of subclinical symptom scales (ADHD, psychosis, depression, and general psychopathology) with the resulting striatal connectivity age-deviation scores were then tested using elastic net (EN) regression. Given the strong contribution of neurodevelopmental factors in susceptibility to neurodevelopmental and psychiatric disorders, it was hypothesized that developing striatal connections would be predictive of clinical symptom domains in the general population. We further expected that those connections predictive of general psychopathology would overlap with those of other symptom domains, but that uniquely predictive connections for each symptom domain would also be identified.

METHODS AND MATERIALS

Participants

Participants were 926 children and adults, 8 to 22 years of age, from a community sample drawn from two publicly available databases. Resting-state functional MRI and T1-weighted scans were collected from eight sites for the Pediatric Imaging, Neurocognition, and Genetics (PING) study (http://ping.chd.ucsd.edu/) (50) and one site for the Philadelphia Neuroimaging Cohort (PNC) (51). Informed consent was acquired by each site according to each study's protocol. Participants were excluded from analyses for the following reasons: incomplete covariate information, framewise displacement (FD) $\geq$0.5 mm, or postscrubbed scan length $\leq$4 minutes. Table 1 summarizes each site's resting-state scan acquisition and participant information for the final study sample.

Neuroimaging Data Analysis

Details of the neuroimaging data preprocessing and nuisance regression is described in the Supplement. Time-courses were extracted for three caudate and three putamen 4-mm seeds, which represented functionally distinct anatomical subregions of the striatum (1). Full-brain connectivity maps for each seed were the Fisher Z transformation of the Pearson r correlation at each voxel. General linear models assessed the linear and nonlinear effects of age, while covarying for sex, FD-DVARS correlations, FD-DVARS^2, scrubbed scan length, and acquisition site. Site was accounted for with one regressor per PING study site, which consisted of ones for those participants scanned at that acquisition site and zeros for all other participants. Connections showing a significant relationship with age were identified as those with a voxel-level and cluster-level threshold of $p < .001$ (52,53). The cluster-level threshold was then multiple-comparisons corrected for the six seeds (i.e., $p < .001/6 = p < 1.67 \times 10^{-4}$). Follow-up analyses examined sex and age-by-sex interaction effects to determine whether striatal connections were significantly different between male and female subjects.

Growth Charting of Developing Connections

Peak coordinates in the age statistical maps were defined as local maxima separated by >15 mm. Four-millimeter seeds were placed around each of these peak ARCs, Fisher Z-transformed connectivity values were extracted, and growth charting was performed. This involved first regressing out the effects of

Table 1. Demographic and Scanner Information for the One PNC Site and the Eight PING Sites

		Demographics				Scanner					
Study	Site	*n*	Male, %	Age, Years	Age Range, Years	Manufacturer	Model	MR Strength	Repetition Time, s	Volumes	Scan Length (Minutes:Seconds)
PNC	1	601	44	15.74 ± 3.08	8–23	Siemens[a]	TrioTim	3T	3.0	126	6:18
PING	2	50	46	16.24 ± 3.16	9–21	Siemens	TrioTim	3T	3.0	128	6:24
PING	3	41	44	18.45 ± 2.68	9–21	Siemens	TrioTim	3T	2.0	300	10:00
PING	4	13	69	14.99 ± 3.48	10–21	Siemens	TrioTim	3T	3.0	128	6:24
PING	5	59	46	15.68 ± 3.38	8–21	Siemens	TrioTim	3T	3.0	128	6:24
PING	6	62	37	16.07 ± 3.73	8–21	Philips[b]	Achieva	3T	2.5	156	6:30
PING	7	17	35	14.21 ± 2.97	8–18	Siemens	TrioTim	3T	2.0	180	6:00
PING	8	31	45	15.76 ± 3.22	8–21	Philips	Achieva	3T	2.5	156	6:30
PING	9	52	46	14.46 ± 4.56	8–21	Siemens	TrioTim	3T	3.0	128	6:24
Total		926	44	15.79 ± 3.30	8–23						

MR, magnetic resonance; PING, Pediatric Imaging, Neurocognition, and Genetics; PNC, Philadelphia Neuroimaging Cohort.
[a]Siemens Medical Solutions, Erlangen, Germany.
[b]Philips Medical Systems, Hamburg, Germany.

sex, FD-DVARS correlations, FD-DVARS^2, scrubbed scan length, and acquisition site (see the Supplement for detailed assessment of site effects). Age was then fit to the full sample of 926 participants. A polynomial model of age, $y = \beta_0 + \beta_1 \times \text{age} + \beta_2 \times \text{age}^2$, was fit to the connectivity measures using the R software, version 3.5.0, package *nls2* (R Foundation for Statistical Computing, Vienna, Austria). For each of the ARCs, age trajectories corresponding to the 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97.5th percentiles were created. This was done by first binning the age variable with a bin size of 1 year, obtaining the quantiles for a given age bin, and then applying the quadratic model of age to each quantile.

Identifying Age-Normative Striatal Patterns

Each participant's age-deviation score was the distance from the 50th percentile fit, with positive age-deviation scores falling above the age-normative fit line and negative age-deviation scores falling below the age-normative fit line. Age-deviation scores for each ARC were then entered into EN regression models to identify those connections in which distance from the age-normative fit was associated with symptom severity in the four symptom domains: ADHD, psychosis, depression, and general psychopathology. While age-normative fit was determined in the full sample, associations with clinical symptom severity were examined exclusively in the PNC sample.

Assessing Symptom Severity in the PNC Sample

As part of the PNC protocol (51), participants underwent a computerized battery assessing almost 600 demographic, medical, and psychopathology items based on the Kiddie Schedule for Affective Disorders and Schizophrenia (54). For the current study, ADHD, psychosis, depression, and general psychopathology domains were examined to determine their relationship with age-normative striatal connectivity. The particular items used for each of the symptom scales were previously described by Kaufmann *et al.* (55). Scores reflected the sum across all items within each scale.

EN Models Assessing Age-Normative Striatal Connectivity Related to Clinical Symptoms in the PNC Sample

EN is a form of regularized regression (56), which minimizes the following function:

$$\min_{\beta_0,\beta_i} \frac{1}{N} \sum_{i=1}^{N} l(y, \beta_0 + \beta_i x_i) + \lambda \left[\frac{(1-\alpha)||\beta||_2^2}{2} + \alpha||\beta||_1 \right]$$

where y is the dependent variable (i.e., clinical symptom scores), x_i are the predictor variables (i.e., age-deviation scores for each ARC), β_i are the regression coefficients, λ is the regularization penalty, and α is the elastic net mixing parameter, which varies between 0 and 1, with lower values favoring the L2 norm penalty (i.e., ridge regression) and higher values favoring the L1 norm penalty (i.e., lasso regression). Negative binomial EN models were implemented using R software.

EN models were fit at five values of α (i.e., 0.001, 0.25, 0.5, 0.75, and 1) and 100 values of λ. Tenfold cross validation was performed in which folds were kept constant across all models. The optimal model fit was assessed using the cross-validated log likelihood across the 10 folds (i.e., the mean log likelihood across the folds), and the optimal model was identified as the one with the maximum cross-validated log likelihood. Additional assessment of the optimal EN model was done by examining stability of the EN model selection across different folds and by examining concordance of the EN variable selection with a second machine learning method, connectome-based predictive modeling (CPM) (57). These additional assessments are described in detail in the Supplement.

RESULTS

From the regression analyses examining striatal development across the full sample, a set of 231 ARCs was identified. Figure 1 displays the significant linear and nonlinear age effects for each of the striatal subdivisions. Analyses performed both with and without global signal regression yielded similar results for both developmental trends and symptom

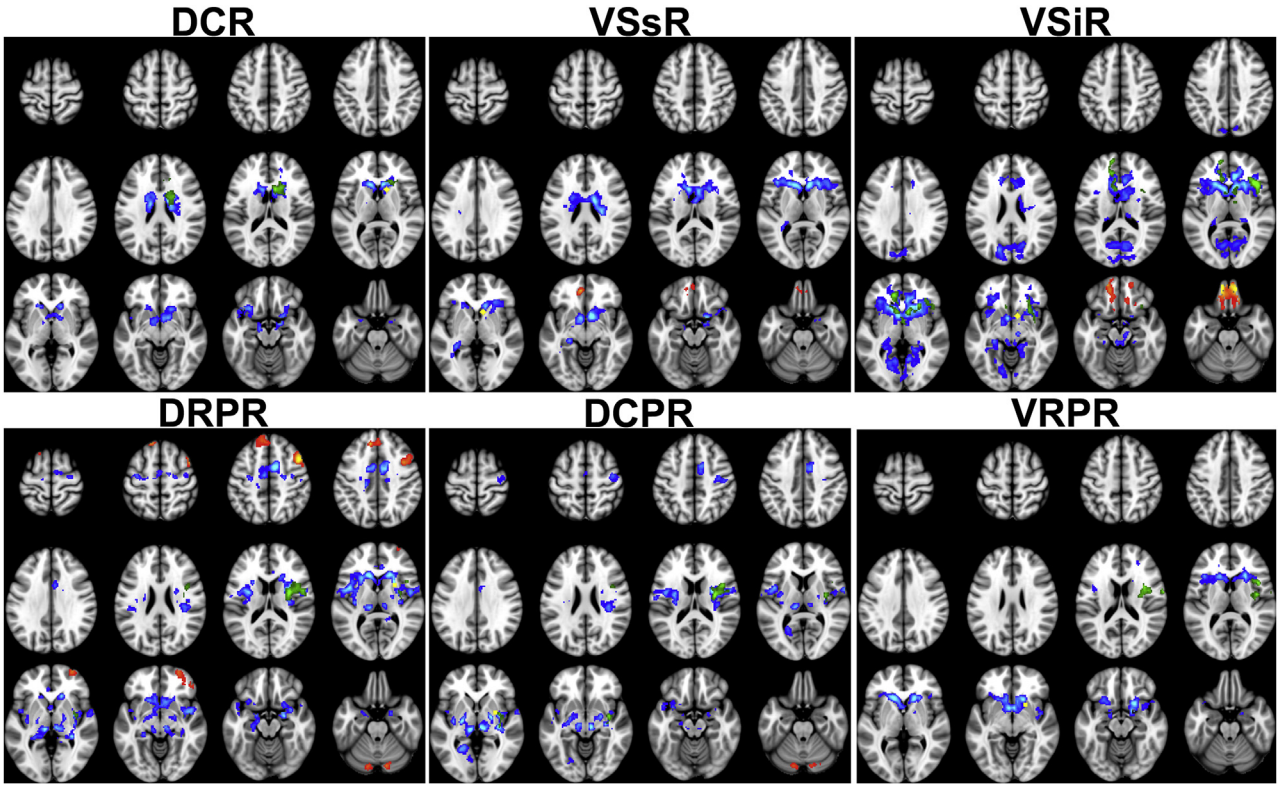

Figure 1. Significant age effects ($p < 1.67 \times 10^{-4}$) for the six striatal seeds: dorsal caudate right (DCR), ventral striatum superior right (VSsR), ventral striatum inferior right (VSiR), dorsal rostral putamen right (DRPR), dorsal caudal putamen right (DCPR), ventral rostral putamen right (VRPR). Positive linear age effects are in red. Negative linear age effects are in blue. Nonlinear age^2 effects are in green. The striatal seed is in yellow. The top row displays the three caudate seeds and the bottom row displays the three putamen seeds.

associations. Global signal is used for the remainder of this article. No significant sex or age-by-sex interaction effects were found.

Growth Charting

The 231 peak coordinates in which significant age effects occurred are listed in Supplemental Table S1. Growth charting was performed on the connectivity values of each of these 231 ARCs. Figure 2 displays developmental effects of two example striatal seeds and the growth charting normative age fits for several of the peak coordinates. Various developmental trends were identified including linear increases and linear decreases with age, as well as nonlinear effects in which connectivity peaked during early or late adolescence. Importantly, the growth-charting approach permitted the calculation of each individual's age-deviation score for each ARC, which was then used in subsequent analyses. Assessment of site effects revealed that there was no significant impact of acquisition site on connectivity values after confound regression (see the Supplement for more discussion of site effects).

Optimal EN Model Selection

Table 2 lists the α and λ values for the optimal model for each of the four clinical symptom scales. The mean and standard deviation of the cross-validated log-likelihood is reported across the 10 times that the optimal model was rerun with varying folds. The log likelihood was very stable over the 10 runs for all symptom scales. Model fit for depression was the most variable over runs, but the variation in log-likelihood values was still very low for this model (i.e., coefficient of variation $0.24/-90.61 = -0.0027$). Therefore, the optimal model fit for all clinical symptom scales was very stable over varying cross-validation folds.

A second method, CPM (57), was applied to assess the validity of the variable selection for the optimal EN models. For this method, a threshold of $p < .10$ on 95% of iterations was used to select predictive connections. Associations between striatal ARCs and clinical symptoms were also required to be in the same direction (i.e., positive or negative associations) on all suprathreshold iterations. CPM selected fewer connections than EN regression for ADHD (23 for CPM, 35 for EN), depression (10 for CPM, 42 for EN), and general psychopathology (20 for CPM, 21 for EN). For each of these symptom sets, the connections resulting from CPM were 100% concordant with those emerging from EN. However, for psychosis, many more connections were selected using CPM (32 for CPM, 8 for EN). Nonetheless, all eight EN connections were also selected using the CPM method. Supplemental Table S2 lists the particular connections that were selected for each method.

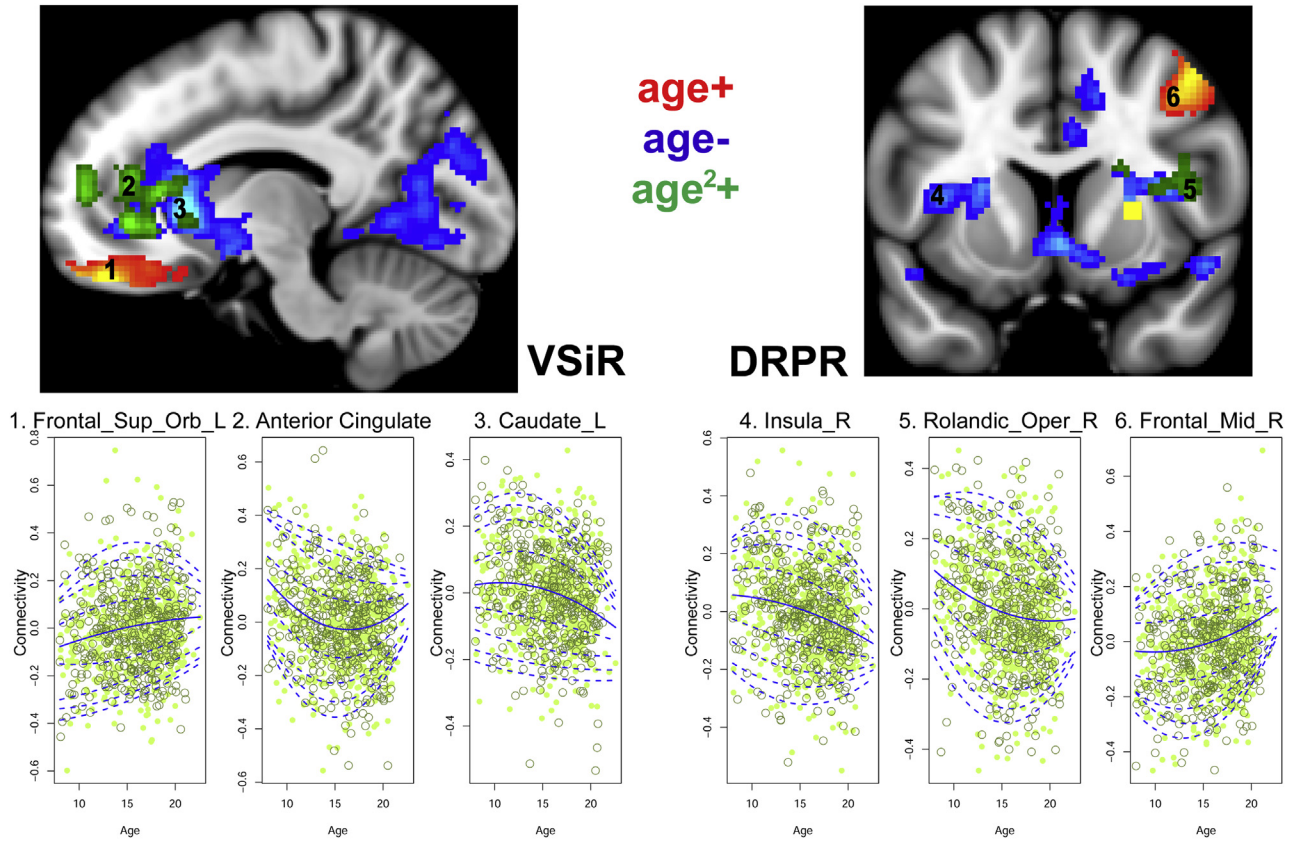

Figure 2. Significant age effects ($p < 1.67 \times 10^{-4}$) and growth charts for two example striatal seeds: ventral striatum inferior right (VSiR) and dorsal rostral putamen right (DRPR). The top row shows significant age effects for VSiR and DRPR. Positive linear age effects are in red. Negative linear age effects are in blue. Nonlinear age^2 effects are in green. The striatal seed is in yellow. The bottom row shows the growth charts for several of the age-related connections: the three on the left display VSiR age-related connections and the three on the right display DRPR age-related connections. Each green dot represents one participant; open, dark green dots are female subjects and closed, light green dots are male subjects. The solid blue line is the 50th percentile fit (i.e., the age-normative fit line) and the dashed lines represent the 2.5th, 5th, 10th, 25th, 75th, 90th, 95th, and 97.5th percentile fits. L, left; Mid, middle; Oper, operculum; Orb, orbital; R, right; Sup, superior.

Clinical Symptoms Relate to Striatal Maturity

Figure 3 displays the selected connections (i.e., those connections with nonzero β values) for the optimal models and their penalized β values for each of the four symptom scales. Each β value was corrected for age (i.e., multiplied by the direction of the linear age effect) so that negative values reflected developmentally delayed and positive values reflected developmentally accelerated associations.

For ADHD symptoms, associated connections included several dorsal putamen–insula connections, all of which were developmentally accelerated with ADHD severity. Conversely, the ventral striatum inferior right–bilateral inferior frontal trigeminal cortex (Brodmann area 45) tended to be developmentally delayed, along with a dorsal caudal putamen right–anterior cingulate gyrus connection, and several connections within the ventral striatum. Connections between the ventral striatum inferior right and subcortical regions, including the globus pallidus, substantia nigra, thalamus, and brainstem, tended to be developmentally accelerated in youths with more ADHD symptoms.

For psychosis symptoms, associated connections were limited to several putamen–anterior temporal pole connections, a putamen–orbitofrontal cortex (OFC) connection (Brodmann area 25), a ventral striatum–medial prefrontal cortex connection, and a couple of dorsal putamen–posterior insula connections. All predictive connections reflected accelerated development in those children with psychosis symptoms. Conversely, depression was characterized by accelerated development of subgenual cingulate connectivity as well as several subcortical limbic regions, including the hippocampus, substantia nigra, globus pallidus, brainstem, thalamus, and

Table 2. Elastic Net Parameters and Log Likelihood for the Optimal Model Predicting Each of the Four Symptom Domains

	α	λ	Log Likelihood
ADHD	0.0001	414.41	−128.20 ± 0.04
Psychosis	0.25	0.25	−193.38 ± 0.08
Depression	0.25	0.13	−90.61 ± 0.24
General Psychopathology	0.0001	766.58	−258.36 ± 0.05

ADHD, attention-deficit/hyperactivity disorder.

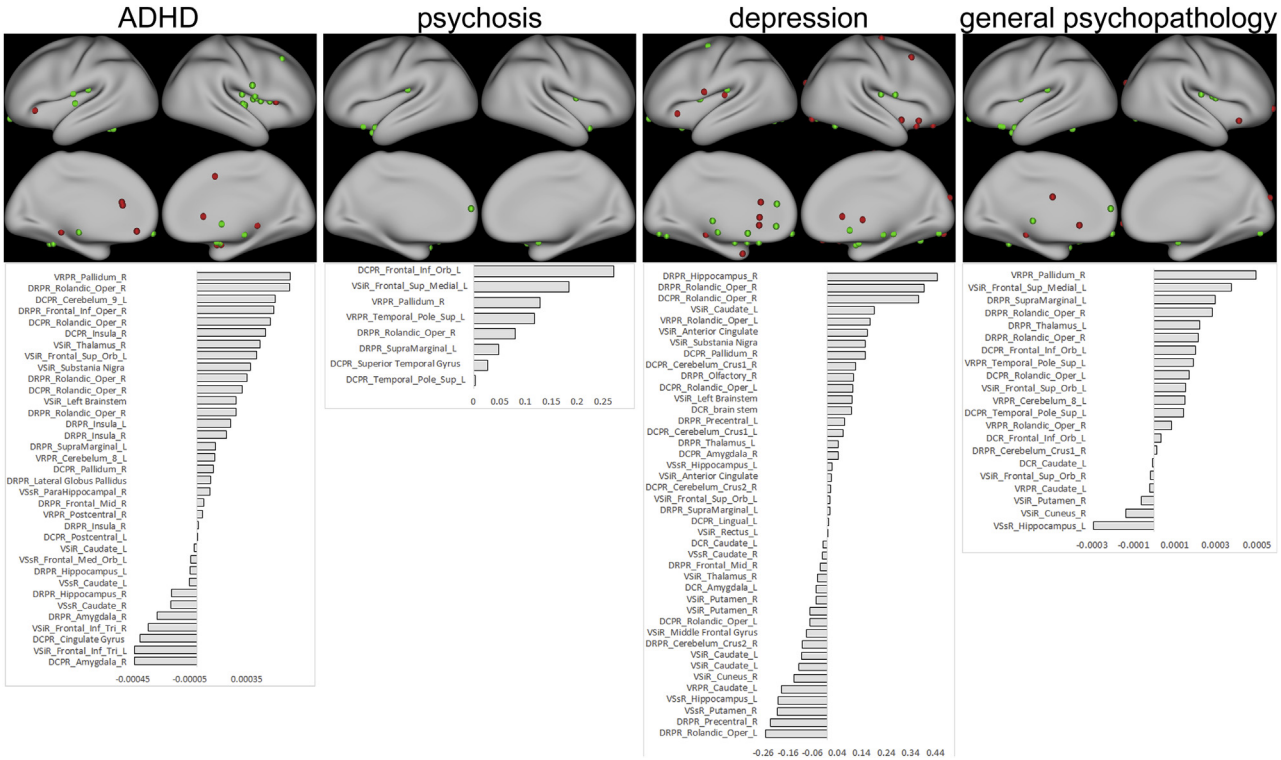

Figure 3. Connections with symptom associations. The peak age-related connections (ARCs) with nonzero βs in the elastic net models are shown in the top row. Those ARCs in which greater symptom severity is associated with age-accelerated connectivity are displayed in green, while those ARCs in which greater symptom severity is associated with age-delayed connectivity are displayed in red. The ARC labels and the age-adjusted βs from the optimal elastic net model are shown in the bottom row. ADHD, attention-deficit/hyperactivity disorder; DCPR, dorsal caudal putamen right; DCR, dorsal caudate right; DRPR, dorsal rostral putamen right; Inf, inferior; L, left; Med, medial; Mid, middle; Oper, operculum; Orb, orbital; R, right; Sup, superior; Tri, triangularis; VRPR, ventral rostral putamen right; VSiR, ventral striatum inferior right; VSsR, ventral striatum superior right.

amygdala. Several intrastriatal connections, on the other hand, tended to be delayed with more depressive symptoms.

For general psychopathology, putamen–dorsal posterior insula connections tended to be developmentally accelerated. Putamen connections to subcortical regions, such as the globus pallidus and thalamus, were also accelerated, whereas intrastriatal connections were delayed. Caudate–medial prefrontal cortex/OFC and putamen–anterior temporal pole connections, which were developmentally accelerated with psychosis, were likewise accelerated with general psychopathology.

EN Model Fit and CPM Prediction

The optimal models emerging from the EN analysis accounted for 6% to 13% of the variance in symptom scores (ADHD [R^2 = .10], psychosis [R^2 = .060], depression [R^2 = .13], general psychopathology [R^2 = .083]). For ADHD and depression scores, the majority of connections selected were unique to those clinical scores, while the majority of connections selected for the psychosis and general psychopathology scores were common to other symptom subscales. Figure 4 displays the association between the fitted values for the optimal EN models and the actual clinical symptom scores. To assess the reliability of these results using a different approach, the CPM method was used to generate prediction for the left-out participant during each iteration of the leave-one-out cross-validation. Consistent with the EN results, the CPM test data resulted in significant prediction for all four clinical domains: ADHD (R^2 = .1025, p = 8.88 × 10^{-16}), psychosis (R^2 = .0070, p = .040), depression (R^2 = .0119, p = .0074), and general psychopathology (R^2 = .0192, p = 6.61 × 10^{-4}).

DISCUSSION

The current study examined the maturation of striatal functional subdivisions in 926 youths ranging from 8 to 22 years of age. The large sample size and broad developmental range allowed for improved characterization of linear and nonlinear age effects on striatal connectivity. While general decreases in intrastriatal and striatolimbic connectivity were observed across all seeds, a number of previously unreported cortical and cerebellar ARCs showed specific maturational patterns for different striatal subdivisions. EN models identified age-inappropriate striatal connectivity that was associated with symptom dimensions in the general population. Consistent with well-established pathophysiology of ADHD (58,59), inferior frontal, insula, and anterior cingulate connections were among the most predictive of ADHD symptoms. Likewise, connections associated with psychosis and depression were consistent with known pathophysiology for each of these

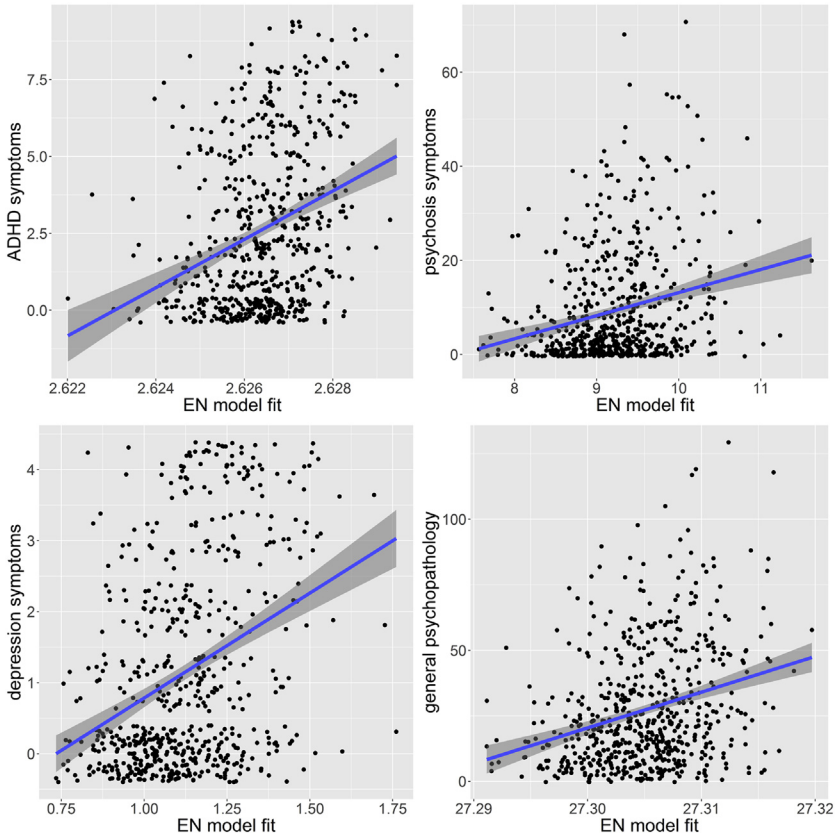

Figure 4. Association between the actual dimensional symptom scores and the elastic net (EN) fitted values. The EN fit accounts for 10.0%, 6.0%, 13.0%, and 8.3% of the variance for attention-deficit/hyperactivity disorder (ADHD), psychosis, depression, and general psychopathology, respectively.

disorders. Medial prefrontal and superior temporal pole connections were predictive of psychosis, while limbic connections were predictive of depression. Connections associated with general psychopathology mostly overlapped with those of other symptom dimensions, notably for the dorsal posterior insula as well as for subcortical and medial prefrontal connections.

Maturation of Striatal Connections

Several developmental trends in striatal connectivity across the brain were identified. The majority of striatal ARCs decreased connectivity with development, particularly for subcortical, motor, visual, and limbic structures, suggesting that the striatum plays a more integral role in establishing motor and limbic circuits early in development but a lesser role later on. Future research is needed to establish why this developmental shift occurs. Potential mechanisms include greater neural recruitment early in development necessary for learning, synaptic pruning of striatal connections, and/or changing dopamine concentrations.

Several developmentally decreasing connections, such as intrastriatal and striatolimbic, were nonspecific, occurring across all striatal functional subdivisions. Other changes were, however, functionally specific. For example, all putamen seeds increased connectivity with the cerebellar lobules crus I and crus II, which are involved in higher-level cognition and are interconnected with the default mode and frontoparietal networks (60–62). All putamen seeds also decreased connectivity with a spatially distributed set of regions subserving basic motor control. This developmental reorganization suggests that the putamen is involved in establishing basic motor control early in development, but becomes more integral to circuits involved in higher-level cognition later.

Functionally distinct developmental trends were found for striatal–ACC connections. Caudate seeds decreased connectivity with the rostral/pregenual ACC, which is commonly implicated in social and emotional aspects of cognition (63–65). Putamen seeds, on the other hand, decreased connectivity with the dorsal ACC, which is recruited for a variety of motor and executive function tasks and is in circuit with sensorimotor and cognitive control networks (66–68). Regional specificity likewise occurred in the reorganization of striatal–OFC connections, including developmental decreases with the posterior OFC across all striatal subdivisions and developmental increases specifically between the ventral striatum and anterior OFC. While a number of studies have documented developmental changes in striatal–OFC connectivity between childhood and early adulthood (13–15), the finding that ventral striatum–anterior OFC connectivity strengthens is novel. Maturation of striatal–OFC circuits is consistent with previous literature documenting the development of reward and emotion-regulation circuitry through adolescence and young

adulthood (69,70). The current findings reveal previously undiscovered specificity in the development of distinct striatal circuitry.

Developing Striatal Connections Are Significantly Associated With Clinical Domains

Striatal maturation plays a critical role in the emergence of neurodevelopmental and psychiatric disorders (8,18,28,39). The current study is the first to distinguish striatal developmental patterns associated with specific clinical dimensions. This study is one of a growing number linking large-scale connectivity patterns with clinical symptom domains in developmental cohorts (46,55,71). Unlike previous research, the current study focused on the striatum and employed a novel approach in which the search for indicative connections was restricted to those showing robust developmental effects. This approach was based on a body of research identifying developmental factors that impact striatal function and potentially lead to the emergence of neurodevelopmental, psychotic, and mood disorders (8–10). As expected, the current study identified a set of ARCs associated with each symptom domain.

A critical question in linking brain function to clinical domains is whether meaningful distinctions between different domains exist. The current findings implicate both unique and overlapping connections for each clinical domain. Previous factor analyses across diagnostic items suggest that a single "p" factor indicating severity of general psychopathology explains common variance across different clinical domains (43,44). Indeed, recent studies examining associations between cortical networks and clinical domains have found that those connections that are predictive of individual domains are likewise predictive of psychopathology more generally (46,55). However, distinct cortical connections have also been recently associated with individual symptom domains (71). Most of the connections that were associated with general psychopathology overlapped with those identified for other domains (i.e., 16 of 21 general psychopathology connections overlapped with other domains). Further, the overlapping connections were those most strongly predictive of general psychopathology, and in all cases, they showed the same direction of effect (i.e., developmentally delayed or developmentally advanced) for each of predicted domains. Notably, the dorsal posterior insula (i.e., Rolandic operculum) emerged as a particular locus associated with psychopathology across all domains. This granular region is commonly implicated in sensorimotor interoception (72–75), particularly to cardiac information (76), which is disrupted during stress (77,78). It is integral to the processing of painful stimuli (79–81), encodes representations for social rejection (82), and may thereby be a general indicator of negative visceral and/or affective internal states (83). Putamen–dorsal posterior insula connections were associated with psychopathology across all four domains and included both overlapping and unique connections for each of the domains. Furthermore, the nearby left supramarginal gyrus was the only single connection associated with all four symptom dimensions. The results suggest that putamen–dorsal posterior insula connectivity is a biomarker of general psychopathology, which reflects elevated social and/or somatic distress associated with greater symptom severity.

Uniquely predictive connections were found for ADHD and depression symptom domains. Consistent with findings of altered function in the anterior insula (59,84,85) and abnormally enhanced connectivity within the cingulo-opercular and/or salience networks in individuals with ADHD (86–88), developmentally accelerated connectivity in several middle and anterior dorsal insula regions was associated with greater ADHD symptom severity. However, developmentally delayed connectivity with the nearby bilateral inferior frontal gyrus (Brodmann area 45) was associated with greater ADHD symptom severity, consistent with the well-established role of this region in inhibitory control dysfunction in ADHD (29,59), and its upregulation with stimulant medication (89).

Limbic structures that are integral to the pathophysiology of depression were associated with depression symptomology. Accelerated maturation with the posterior OFC (i.e., subgenual cingulate) was uniquely predictive of depression, which is in line with the role of the subgenual cingulate in affective processing and emotion regulation, as well as with its altered function in major depressive disorder (12,90,91). Other subcortical limbic structures that were predictive of depression, such as the hippocampus and amygdala, likewise play a critical role in affective processing in depression (92).

Unlike the other symptom domains, most of the connections associated with psychosis were also related to general psychopathology (i.e., seven of eight connections). This included several medial prefrontal and superior temporal gyrus connections, which, while predictive of general psychopathology, were not predictive of ADHD or depressive symptoms. This overlap in the neural substrates of psychosis and general psychopathology is in line with previous characterizations suggesting that psychosis is indicative of more severe psychopathology than other symptom domains (44). Dysfunction in the medial prefrontal cortex, a core part of the default mode network, is commonly found in psychotic individuals (93–95), as is dysfunction in the superior temporal gyrus (31,96–98).

The current study examined striatal maturation in a cross-sectional sample, spanning 8 to 22 years of age, taken from the general population. This is the largest such developmental study of striatal connectivity to date, and the growth-charting approach allowed for the identification of age-inappropriate striatal connectivity associated with ADHD, psychosis, depression, and general psychopathology. Future studies may improve characterization of striatal ARCs by employing a longitudinal study design, which could detect individual differences in developmental trajectories. Nonetheless, the present approach of examining age deviation in striatal ARCs was successful for selecting predictive ARCs and accounted for a relatively high proportion of the variance. Thus, the EN models provided a powerful method for detecting atypical age-related connectivity associated with several clinical symptom domains. Identification of such clinical biomarkers in the general population may be disadvantageous compared with case-control studies owing to reduced symptom variability and smaller effect sizes. However, it is also advantageous, in that it is robust to clinical confounds such as medication and it may identify early indicators of clinical risk. In summary, the current study found novel developmental trends in

striatal connectivity, which lend insight into the maturation of reward-related, emotional, and cognitive functions. Novel findings of distinct striatal ARCs associated with ADHD, psychosis, and depression symptoms reveals distinct neurodevelopmental pathways for these domains. Identification of such pathways may indicate early clinical risk and provide clues for disease prevention.

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