

ORIGINAL ARTICLE

Inter-Individual Differences in Striatal Connectivity Is Related to Executive Function Through Fronto-Parietal Connectivity

Fahimeh Darki¹, Bruno Sauce¹, Torkel Klingberg^{1,*} and for the Pediatric Imaging, Neurocognition, and Genetics Study²

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Address correspondence to Torkel Klingberg, Department of Neuroscience, Karolinska Institutet, Solnavägen 9, 171 65 Solna, Stockholm, Sweden. Email: torkel.klingberg@ki.se.

Abstract

The striatum has long been associated with cognitive functions, but the mechanisms behind this are still unclear. Here we tested a new hypothesis that the striatum contributes to executive function (EF) by strengthening cortico-cortical connections. Striatal connectivity was evaluated by measuring the resting-state functional connectivity between ventral and dorsal striatum in 570 individuals, aged 3–20 years. Using structural equation modeling, we found that inter-individual differences in striatal connectivity had an indirect effect (via fronto-parietal functional connectivity) and a direct effect on a compound EF measure of working memory, inhibition, and set-shifting/flexibility. The effect of fronto-parietal connectivity on cognition did not depend on age: the influence was as strong in older as younger children. In contrast, striatal connectivity was closely related to changes in cognitive ability during childhood development, suggesting a specific role of the striatum in cognitive plasticity. These results support a new principle for striatal functioning, according to which striatum promotes cognitive development by strengthening of cortico-cortical connectivity.

Key words: development, executive function, Pediatric Imaging, Neurocognition, and Genetics (PING), resting-state fMRI, structural equation modeling (SEM)

Introduction

The striatum is implicated in motivation (Schultz et al. 1997), implicit learning (Packard and Knowlton 2002; Graybiel 2008), and executive functions (EFs) such as working memory (WM), inhibitory control, and set-shifting/flexibility (Postle and D'Esposito 1999; Grahn et al. 2008; McNab and Klingberg 2008). EF is associated with activity predominantly located in

the dorsal striatum (DS) (Grahn et al. 2008), whereas the ventral striatum (VS) is more related to motivation and anticipation of rewards (Postle and D'Esposito 1999). Though these associations have been known for a long time, there is still a need for models describing the neural mechanisms of how the striatum supports EF.

Although there are models for striatal involvement in reinforcement learning (Montague et al. 1996; Collins and Frank

2014), and proposed mechanisms underlying updating in WM (Hazy et al. 2007), it is still unclear how striatum supports a wider range of cognitive functions, how it relates to cortical networks, and what is its role in cognitive development. Here, our goal was to test a new hypothesis, according to which the striatum affects EF by strengthening cortico-cortical functional connectivity.

Cognitive abilities, as most cortical functions, are not implemented in an isolated, single cortical area, but a network of areas. The efficiency of such a network depends on the strength of its connectivity. Importantly, the functional connectivity measured during task performance is closely related to that during rest (Cole et al. 2014), for example, for WM, higher capacity is related to higher synchronicity of frontal and parietal activity (Palva et al. 2010). Regarding childhood development, recent evidence shows that gradual slow changes in network connectivity over the years are linked to changes in EF (see Luna et al. 2015 for a comprehensive review on this topic). Functional network organization at early ages undergo developmental modifications toward more specialized networks and a greater systems-level integration (Luna et al. 2015). For example, the improvement of WM during childhood over the years is associated with increased fronto-parietal connectivity during rest (Fair et al. 2007; Sherman et al. 2014), presumably due to the strengthening of synaptic connectivity. Similarly, the increase in WM capacity through training is associated with increased fronto-parietal connectivity (Kundu et al. 2013), and an increase in resting-state connectivity (Takeuchi et al. 2010; Jolles et al. 2013; Takeuchi et al. 2013; Astle et al. 2015). Strengthening of cortico-cortical connectivity is therefore a possible mechanism behind the improvement of EF.

The connections between separate parts of cortex and striatum usually form parallel loops (Alexander and Crutcher 1990). Interestingly, however, there is also evidence for converging projections, where different cortical regions project to overlapping parts of the striatum, identified with tract tracing in macaque monkeys (Choi et al. 2017), as well as functional (Choi et al. 2012; Choi et al. 2017) and structural imaging in humans (Jarbo and Verstynen 2015; Darki et al. 2018). Such converging regions are by their connectivity in a position to integrate and strengthen cortico-cortical connections. In support of this, we previously found that microstructure of a convergence region of the DS is more highly associated with WM capacity than nonconvergence regions (Darki et al. 2018).

The VS influences the DS by spiraling, dopaminergic connections via the ventral tegmental area (VTA), and substantia nigra (SN) (Haber et al. 2000). This ventral–dorsal interactivity might be crucial for striatal function, and is implicated in habitual drug dependence (Everitt and Robbins 2005; Belin and Everitt 2008) as well as skill learning (Atallah et al. 2007). It was recently shown that inter-individual differences in the connectivity between VS and DS can be measured at rest in humans, and that this connectivity is increased by administration of a dopamine D2-agonist (Piray et al. 2017).

We analyzed resting-state activity data from the Pediatric Imaging, Neurocognition, and Genetics (PING) Study, which included a large cohort of children, adolescents, and young adults, between the ages of 3 and 20 years (Jernigan et al. 2016). Correlation of activity between VS and DS at rest was measured as an indicator of striatal connectivity. We also measured the correlation between an intraparietal and a prefrontal cortical area, which are activated during WM performance (Dumontheil et al. 2011) and are located within the dorsal attention network (Yeo et al. 2011), and might thus play a more general role in

cognitive control (Friedman et al. 2008; Cole et al. 2014; Reineberg et al. 2015). Our hypothesis was that striatal connectivity would affect fronto-parietal connectivity, which in turn would be related to EF.

In addition to testing our main hypothesis, this sample allowed us to investigate the role of striatum during childhood cognitive development. It is important to distinguish the role of striatum for learning as opposed to performance of learned behavior (Everitt and Robbins 2005; Atallah et al. 2007). Similarly, one can distinguish between capacity (i.e., the level of cognitive capacity at a certain point) versus plasticity (i.e., is the change in capacity over time, during development or cognitive training) and we predicted that striatal connectivity would be more related to plasticity (Klingberg 2014; Klingberg 2016). To test this, we analyzed the bi-variate relation between cognition, striatal connectivity, and age.

Methods

PING resting-state fMRI

Here, we used resting-state fMRI (rs-fMRI) data of the PING Study (<http://ping.chd.ucsd.edu/>). PING was launched in 2009 by the National Institute on Drug Abuse and the Eunice Kennedy Shriver National Institute of Child Health & Human Development as a 2-year project of the American Recovery and Reinvestment Act. The primary goal of PING is to create a data resource of highly standardized and carefully curated MRI data, comprehensive genotyping data, and developmental and neuropsychological assessments for 1493 typically developing children and adolescents aged 3–20 years, from 6 major continental populations (African, Central Asian, East Asian, European, Native American, and Oceanic). The scientific aim of the project is, by openly sharing these data, to amplify the power and productivity of investigations of healthy and disordered development in children and to increase understanding of the origins of variation in neurobehavioral phenotypes. For up-to-date information, see <http://ping.chd.ucsd.edu/>.

The PING imaging dataset was collected using 3 different (3T) scanner manufacturers: GE, Siemens, and Philips. The imaging protocols and the pulse sequence parameters (<http://pingstudy.ucsd.edu/resources/neuroimaging-cores.html>) were optimized to provide equivalent contrast properties (Jernigan et al., 2016). The rs-fMRI volumes of the Siemens scanners were acquired with TR = 3000 ms, TE = 30 ms, and voxel size = 3 * 3 * 3.5 mm; the rs-fMRI volumes of the Philips scanners were acquired with TR = 2500 ms, TE = 30 ms, and voxel size = 2.67 * 2.67 * 3 mm; and the rs-fMRI volumes of the GE scanners were acquired with TR = 3000 ms, TE = 30 ms, and voxel size = 3 * 3 * 3 mm. Subjects were instructed to lay still and fixate on a white cross displaying on a black background.

For our current study, we used the preprocessed rs-fMRI volumes provided by the PING repository. As part of the PING preprocessing pipeline, the volumes were all normalized to standard MNI template after slice timing correction and realignment. Moreover, a spatial smoothing using a Gaussian kernel of 5 mm and a grand-mean intensity normalization of the entire 4D dataset were performed. The rs-fMRI data was inspected for head movement and artifacts, and consequently the mean frame-to-frame parameter was computed. We used the mean-square of the 6 head movement variables as the head movement parameter and included it as a covariate in our statistical analysis. Moreover, the number of rs-fMRI volumes was found to be

different and varied from 19 to 300 volumes across individuals due to the different scanning protocols. We excluded from the analyses the subjects with rs-fMRI volumes less than 50 (number of subjects included = 572, F/M = 289/283). The subjects included in the analysis had either 50, 128, 156, or 300 volumes. We added this difference in number of volumes and the site of data collection as confound variables in our statistical analyses.

Regions of interest selection and functional connectivity

In order to select a region of interest (ROI) in the DS with projections to both frontal and parietal cortices, we performed striatum parcellation on the diffusion tensor imaging (DTI) data of 70 randomly selected subjects from the PING dataset. To find a more accurate anatomical parcellation, we also included 70 randomly selected subjects from the Human Connectome Project (HCP) dataset, which has a higher resolution (Van Essen et al. 2013). The imaging protocols for PING and HCP DTI data are provided in (<http://pingstudy.ucsd.edu/resources/neuroimaging-cores.html>) and (Van Essen et al. 2013), respectively. The diffusion-weighted images were preprocessed using intensity normalization, distortion correction, eddy current, and motion correction (for details see Darki et al. 2018). The entire striatum, including the caudate nucleus, putamen, and the accumbens nucleus, was used as a seed region in a probabilistic fiber tracking to find the striatal regions connected to 7 different cortical regions (i.e., orbitofrontal cortex, dorsolateral prefrontal cortex (DLPFC), parietal cortex (PC), rostral motor, caudal motor, and temporal and occipital regions were selected as classification targets) (Darki et al. 2018). For each individual, the probability of connection to each cortical region was quantified. Each probability map was then thresholded to include only voxels with >15% probability of connection. Next, we superimposed the probability maps from all randomly selected subjects (Fig. 1a), and retained only the voxels that survived in >70% of the individuals. The striatal regions with connections to the main targets of interest (i.e., the DLPFC and the PC) were selected (shown in yellow and red for DLPFC and PC, respectively, in Fig. 1b) and overlaid together to define the convergence region in the striatum with connections to both DLPFC and PC (shown in orange, Fig. 1b). The convergence region within the caudate nucleus was selected as the DS ROI for the functional connectivity analysis (the orange ROI in Fig. 1d). This convergence region did not end up in the VS, instead we anatomically defined the entire nucleus accumbens based on Harvard-Oxford subcortical atlas as the VS ROI (the green ROI in Fig. 1d).

Moreover, we selected the superior frontal and intraparietal cortical regions (i.e., combined inferior and superior parietal) activated during a visuo-spatial WM performance in a typical developmental sample of children and adolescents (Dumontheil et al. 2011) as our cortical ROIs (shown in blue, Fig. 1c and d). These regions previously showed correlations with WM performance during development (Darki and Klingberg 2015). Moreover, these cortical areas overlapped with the frontal and parietal areas previously selected as target regions for striatal convergence ROI selection (Darki et al. 2018) and located within the dorsal attention network (Yeo et al. 2011). As an alternative to select the entire DLPFC and PC, we selected these functionally defined fronto-parietal regions to be more precise in ROI selection (as these regions are involved in EF) and to select rather smaller cortical regions for functional connectivity analysis.

After the ROI selection, the preprocessed rs-fMRI time-series were extracted from all voxels within homologous ROIs in both hemispheres and averaged to create 1 single time-series for each ROI and each individual, separately. Consequently, the functional connections between frontal and parietal ROIs as well as the VS and DS were computed as the full correlations of their time-series for each individual, using FSLnets (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets>), and respectively called as F-P_{fc} and VS-DS_{fc} in the current study.

PING cognitive assessment

We selected 3 specific cognitive assessments among the many conducted by PING using the NIH Toolbox Cognition Battery (Akshoomoff et al. 2014) (<http://www.nihtoolbox.org>). We selected these tasks based on their reliance on critical processes that make up EF (Friedman and Miyake 2017). The tasks were the list-sorting task (designed to assess WM), the flanker task (designed to assess inhibitory control), and the Dimensional Change Card Sort (DCCS; designed to assess set-shifting/flexibility).

In the list-sorting task (Akshoomoff et al. 2014), a series of items were presented on the computer screen both visually and orally, 1 stimulus at a time. Then, the participants were asked to recall the items out loud in order of size in the real world, from smallest to largest. There were 2 conditions in the task: in one, all items were from the same category (e.g., animals), and in the other, the items were mixed from 2 different categories (e.g., animals and food), and participants had to report all stimuli in order of size from 1 category first, and then the other. The number of items in each series increased from 1 trial to the next and the task stopped when the subject failed in 2 trials of the same length. For the list-sorting task, we used the total items correct across all trials as the measure of WM performance.

The flanker task was designed to assess inhibitory control in the context of visual selective attention (Akshoomoff et al. 2014). Participants were required to indicate the left-right orientation of a centrally presented stimulus while inhibiting attention to the potentially incongruent stimuli that surround it (i.e., the flankers, two on either side). The stimuli were arrows pointing left or right (and for young children, the stimuli were fish pointing left or right, so to be more engaging and larger, which makes the task easier). On some trials, the orientation of the flanking stimuli is congruent with the orientation of the central stimulus, and on others it is incongruent. We used here the performance on the incongruent trials. In every trial, participants gave their answers (a choice between left of right arrow) by touching the screen. Scores for the flanker task were created using a 2-vector method (developed by the NIH Toolbox team) that incorporates accuracy and, for participants who maintained a high level of accuracy (>80% correct), response time as well. Each type of score ranged from 0 to 5, for a maximum total score of 10.

The DCCS from NIH Toolbox was designed to assess set-shifting and cognitive flexibility, and it is frequently used to measure EF in young children (Akshoomoff et al. 2014). Participants were shown 2 target cards (e.g., a blue rabbit and a red boat) and asked to sort a series of bivalent test cards (e.g., red rabbits and blue boats) according to either color or shape. Participants gave their answers by touching the screen. Every 5 trials, the rule is changed. Scores for the DCCS were created using the same 2-vector method described above for the flanker task. Each type of score ranged from 0 to 5, for a maximum total score of 10.

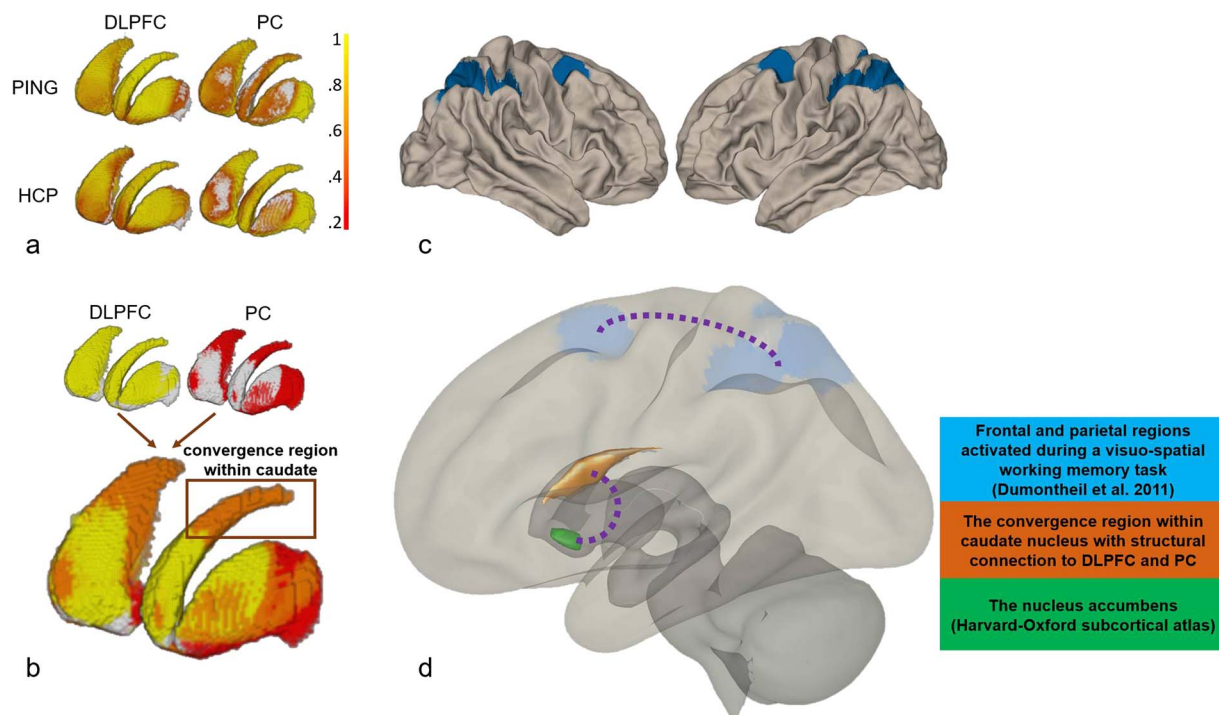


Figure 1. (a) Group map of striatal regions with connections to the DLPFC and the PC across all subjects thresholded at the probable value of .15 in individual space for both PING and HCP subsamples. The group maps are thresholded at 20% of all subjects to display the connected regions that are consistent in at least 20% of participants and the color bar indicates the percentage of the number of subjects. (b) The convergence region (orange) in DS based on the overlaps of the striatal areas receiving connections from DLPFC (yellow) and PC (red) for at least 70% of participants. (c) The frontal and parietal regions of interest (blue) based on activation during a visuo-spatial WM task in children and adolescents (Dumontheil et al. 2011). (d) The cortical ROIs (blue), dorsal striatal convergence region (orange), and the nucleus accumbens (green). Correlations of resting-state functional connectivities were calculated between ventral and dorsal striatum, as well as between the frontal and parietal regions (purple dotted lines).

Statistical analyses

In order to test our hypothesis, we used structural equation modeling (SEM). As a hybrid of multiple regression and factor analysis techniques, SEM allows simultaneous assessment of the strength and direction of the interrelationships among multiple dependent and independent variables, and examines the direct and indirect effects of 1 variable upon another (Kline 2015). Since SEM can have multiple indicators for a single (latent) variable, it reduces measurement error because only the shared variance between measures are considered, leading to more accurate and often stronger relationships between latent variables that is found from other multivariate methods such as MANOVA or multiple regression (Kline 2015). The use of SEM has been well validated for modeling functional connectivity from fMRI (Rogers et al. 2007), and seems to be especially fitting for resting state data (James et al. 2009). Furthermore, SEM has been widely used in brain imaging research on EF (Schlösser et al. 2006).

Using SEM, we tested 2 models of relationships between the variables. The first was a simple model (Fig. 2a) testing the hypothesis that the VS-DS_{fc} influences the F-P_{fc}, which in turn influences the latent construct of EF (as measured by the cognitive assessments of list-sorting, flanker task, and the DCCS). The same hypothesis was also evaluated in a full model (Fig. 2b) but also including effect of age as well as the confounding variables of head movement, site, and number of rs-volumes.

We used the maximum likelihood estimation in AMOS 25 to acquire the solution for our 2 models. This particular estimation

is considered robust in comparison to other procedures like Generalized Least Squares and Asymptotically Distribution-Free estimations, and allows reliable fit indices with relatively small samples (Chou and Bentler 1995). We assessed model fit by using the absolute index of Root Mean Square Error of Approximation (RMSEA), which describes how well the model represents the observed data, and where lower values indicate better fit. RMSEA values of 0.08 and below are considered good (Hu and Bentler 1999). In addition to this absolute index, we also assessed model fit with the incremental index of Comparative Fit Index (CFI). This describes how well the model fits in comparison to a baseline model in which all variables are uncorrelated and without latent variables, and for which higher values indicate better fit (Kline 2015). CFI indicate an adequate model fit at values of 0.95 or above (Hu and Bentler 1999). We chose these tests due to their statistical relevance and frequent use (Schreiber et al. 2006; Hooper et al. 2008; Kline 2015). For assessing the significance of individual parameters such as regression paths and correlations, we chose an alpha value of 0.05.

We tested for the hypothesized interaction effect between age and VS-DS_{fc} on F-P_{fc} in the full model by using the residualized product scores between age and VS-DS_{fc}—a reliable method to test interaction in SEM, as recommended in Lance 1988. We also tested for the indirect effect of VS-DS_{fc} on EF via VS-DS_{fc} in the full model. For that, we used the SEM mediation analysis of bias corrected confidence interval (CI) with 2000 bootstrap iterations and a CI of 95%. In addition, we tested a moderation of gender via chi-square differences by using multigroup analysis in the full model for all paths (i.e., comparing an unconstrained

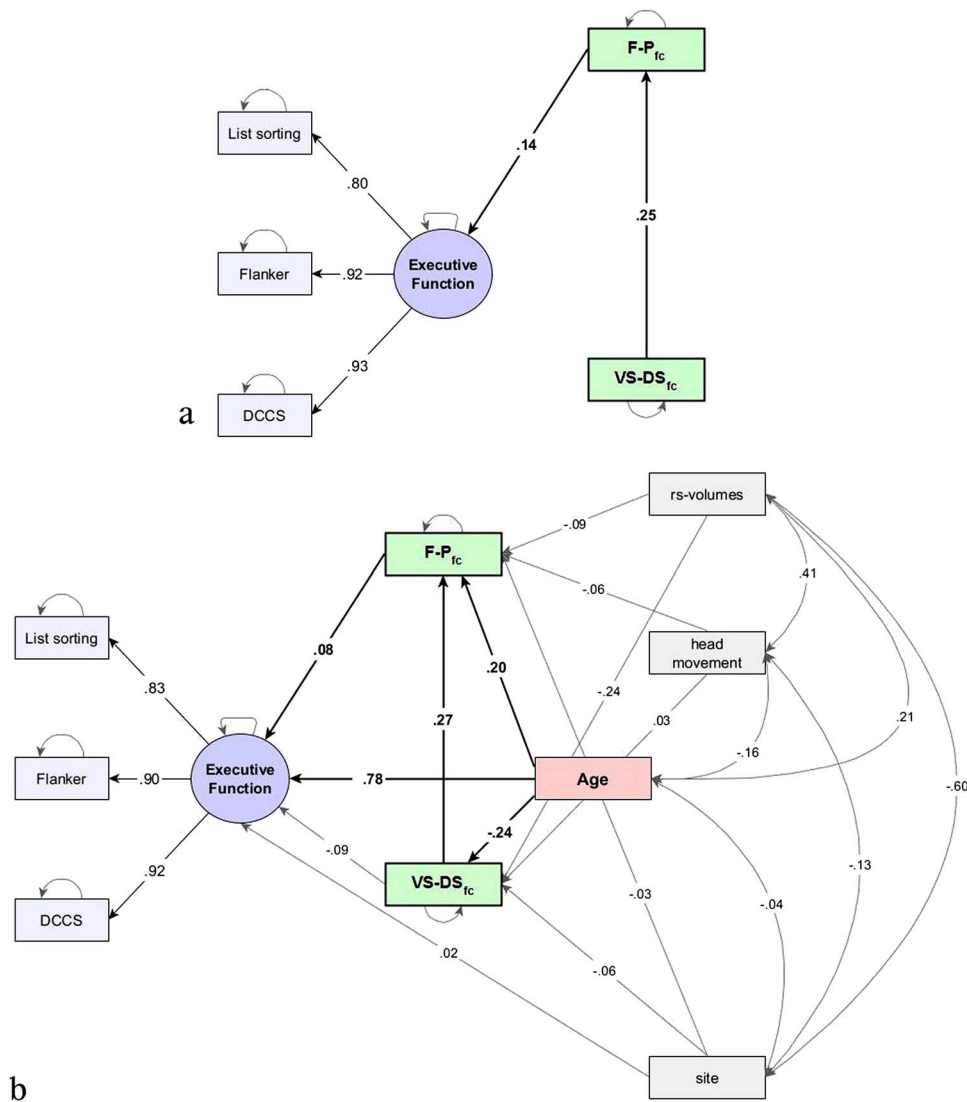


Figure 2. (a) Simple model of the relationship between VS-DS_{fc}, F-P_{fc}, and EF. The model overall had a good fit to the data. Arrows going out of the latent factor (big circle) of EF represent factor loadings, while other straight arrows represent regression weights, and curved double-sided arrows between 2 variables represent correlations. Double-sided arrows going toward the same variables represent error (i.e., leftover variance due to flaws in measurements and estimations). All parameters shown are standardized. (b) Full model of the relationship between VS-DS_{fc}, F-P_{fc}, and EF, and age, including the confounding variables of site, head movement, and rs-volumes. The model overall had a good fit to the data. Arrows going out of the latent factor (big circle) of EF represent factor loadings, while other straight arrows represent regression weights, and curved double-sided arrows between 2 variables represent correlations. Double-sided arrows going toward the same variable represent error. All parameters shown are standardized.

model between genders with a fully constrained model) and for only the most relevant paths (i.e., comparing an unconstrained model between genders with a model constrained only for that particular path or paths).

Because PING is a developmental sample, we performed an independent analysis focusing on the age-related changes for F-P_{fc} and VS-DS_{fc} as well as the age-related improvements in the latent factor for EF. To obtain scores of EF, we used an exploratory factor analysis in SPSS 25 that would be separate from the SEM analyses above (and so could add additional support for the stability of the EF factor). Exploratory factor analysis is a statistical method that describes variability among multiple correlated variables, and captures the variance shared in common between variables (as opposed to techniques such as principal component analyses that capture both shared and nonshared variance,

and are better suited for purposes of dimension reduction). We defined the EF factor as the first factor from the analysis, and extracted the factor scores on EF using the regression method for the following developmental analyses. (A factor score is analogous to an average z score of an individual's performance on all tasks, where the performance on each task is weighted according to the degree of loading on the first factor.)

For the developmental analyses, we compared a linear model ($y = a + b \cdot \text{age}$) of development against an inverse function ($y = a - b/\text{age}$); where the asymptote "a", that is, peak cognitive capacity (EF score) of an individual, approached in the end of cognitive development (the function would not be applicable to the entire life-span). An inverse function has previously been found to be a better model for development of WM during childhood and adolescence (Dumontheil et al. 2011).

Results

SEM analysis indicated that the simple model (Fig. 2a) had a good fit to the data (RMSEA = 0.078; CFI = 0.973). The performance of cognitive tasks showed all significant factor loadings on the latent trait here tentatively called EF, based on prior descriptions (Friedman et al. 2008). Furthermore, the path from the functional connectivity between ventral and dorsal striatum (VS-DS_{fc}) to fronto-parietal functional connectivity (F-P_{fc}) was significant ($\beta = 0.25$, $P < 0.001$), as was the path from F-P_{fc} to EF ($\beta = 0.14$, $P = 0.001$).

The full model included age as well as potential confounding variables (Fig. 2b). This model also showed a good fit (RMSEA = 0.043; CFI = 0.987). As in the simple model, the path from VS-DS_{fc} to F-P_{fc} was significant ($\beta = 0.27$, $P < 0.001$), as was the path from F-P_{fc} to EF ($\beta = 0.08$, $P = 0.006$). Of relationships new to the full model, it is of note that the path from VS-DS_{fc} to EF was significant ($\beta = -0.09$, $P = 0.002$), and that age had significant positive effect on F-P_{fc} ($\beta = 0.20$, $P < 0.001$), and EF ($\beta = 0.78$, $P < 0.001$), and a negative effect on VS-DS_{fc} ($\beta = -0.24$, $P < 0.001$).

Regarding the confounding variables, their role on the study's relevant variables was frequently nonsignificant; except for a significant effect of rs-volumes on VS-DS_{fc} ($\beta = -0.24$, $P < 0.001$). Considered together, the full model explains 68% of the variance in EF in our sample. Meanwhile, a full model with age removed still explains 21% of the variance in EF (since confounds play a small or nonsignificant role, this means that the functional connectivities are able to explain a substantial part of variation beyond age).

Importantly, there was a significant indirect effect of VS-DS_{fc} on EF via F-P_{fc} ($\beta = 0.03$, $P = 0.001$, 95% CI [0.014, 0.043]), which suggests that the role of striatal connectivity to differences in EF occurs in part through its relationship with fronto-parietal connectivity.

There was no significant interaction between age and VS-DS_{fc} on F-P_{fc} ($\beta = 0.1$, $P = 0.837$), which suggests that the effect of VS-DS_{fc} on F-P_{fc} does not depend on differences in age among the participants. For the effect of gender, there was a significant difference between the full model for males and females ($df = 18$, χ^2 difference = 43.80, $P = 0.001$). However, the connections relevant to our hypothesis were significant in both models, and did not differ between genders: VS-DS_{fc} to F-P_{fc} ($df = 1$, χ^2 difference = 0.65, $P = 0.421$; with $\beta = 0.30$ for females and $\beta = 0.22$ for males), F-P_{fc} to EF ($df = 1$, χ^2 difference = 0.17, $P = 0.684$; with $\beta = 0.07$ for females and $\beta = 0.08$ for males).

Furthermore, we tested the full model in SEM with only list-sorting task instead of the latent variable of EF, in order to test if the relationships would also hold specifically for WM (as it might be relevant to the literature). This model showed a good fit (RMSEA < 0.001; CFI = 1.00), and all conclusions from the prior full model with EF still held; of note, a significant path from VS-DS_{fc} to F-P_{fc} ($\beta = 0.27$, $P < 0.001$), as well as the path from F-P_{fc} to WM ($\beta = 0.08$, $P = 0.008$). As in the full model with EF, the full model with WM showed no interaction with age, and similar results for the effect of gender.

In order to explore the specific importance of the functional connectivity of the fronto-parietal regions, we tested the full model in SEM replacing F-P_{fc} by another 2 regions of the cortex: the functional connectivity between the right V1 and the left V1 of the occipital cortex (RV1-LV1_{fc}). This model had a good fit (RMSEA = 0.04; CFI = 0.99) and although the path from VS-DS_{fc} to RV1-LV1_{fc} was significant ($\beta = 0.18$, $P < 0.001$), the path from RV1-LV1_{fc} to EF was not significant ($\beta = -0.4$, $P = 0.109$). This suggests that the VS-DS connectivity does not affect cognition

through any general cortico-cortical connectivity, but might be more specific to particular regions of the cortex, such as F-P.

In an analysis independent from the SEM, we assessed the age-related changes for F-P_{fc} and VS-DS_{fc} as well as the age-related improvements in the latent factor for EF. The exploratory factor analysis resulted in an EF factor accounting for 74.2% of the variance in performance (eigenvalue = 2.23). Performance from the 3 cognitive tasks loaded consistently and in the same direction: the list-sorting task had a loading of 0.78; the flanker task had a loading of 0.89; and the DCCS had a loading of 0.90. Of note, the factor scores from the exploratory factor analysis and the scores from the SEM in the full-model used in previous analyses had an almost perfect correlation ($r = 0.99$, $P < 0.001$)—further showing the stability of the construct of EF based on the PING tasks.

Figure 3a and b shows the development of EF and VS-DS_{fc} over age. The development of EF (the factor scores extracted from the exploratory factor analysis) was significantly described by an inverse function (fit by inverse of age ($y = a - b/\text{age}$): $\beta = -18.03$, $P < 0.001$, 95% CI [-18.6755 to -17.3815]) and was significantly better than a linear function ($y = a + b \cdot \text{age}$) (AIC: 1496.8 for linear and 958.5 for inverse function; BIC: 1510.9 for linear and 972.6 for inverse function). The derivative of the inverse is positive but decreasing quadratically with age (b/age^2). We found that the function $c - d/\text{age}^2$ significantly predicted the development of VS-DS_{fc} over time (fit by inverse of square age: $\beta = 4.53$, $P < 0.001$, 95% CI = [2.93–6.12]). This model was significantly better than a constant model ($F(569) = 31.1$, $P < 0.001$), which is the derivative of a linear function. Therefore, striatal connectivity was related to the change in EF over time, consistent with a role for cognitive plasticity.

In the light of the nonlinear development of EF seen in our developmental analyses, we re-analyzed all SEM models using age inverse (1/age) instead of age as a covariate. The new model with 1/age continued to have a good fit to the data, and all conclusions from the prior analyses still held (e.g., significant association between VS-DS_{fc}, significant association between F-P_{fc} and EF).

Discussion

Using fiber tracking and diffusion weighted imaging, we identified a part of the DS that receives converging projections from both prefrontal and intraparietal cortices. We then measured the correlation between VS and the dorsal convergence region as an index of striatal connectivity. Inter-individual differences in striatal connectivity affected differences in fronto-parietal connectivity, which in turn was positively associated with EF (here, the latent factor in common among tasks tapping WM, inhibition, and set-shifting/flexibility). These results support a model by which striatum affects cognition via the strengthening of cortico-cortical connections.

We also investigated the role of developmental stages in our study. First, our results showed that the effect of striatal connectivity on fronto-parietal connectivity was robust over time: the influence was as strong in older as younger children (i.e., the influence was independent of developmental stages). Similarly, the relationship between fronto-parietal correlation and cognition was also robust over time. In contrast, we found that age differences had a small and significant influence on the functional connectivities between fronto-parietal regions and between striatal regions, as well as a very large influence on EF. These results are in agreement with the general pattern

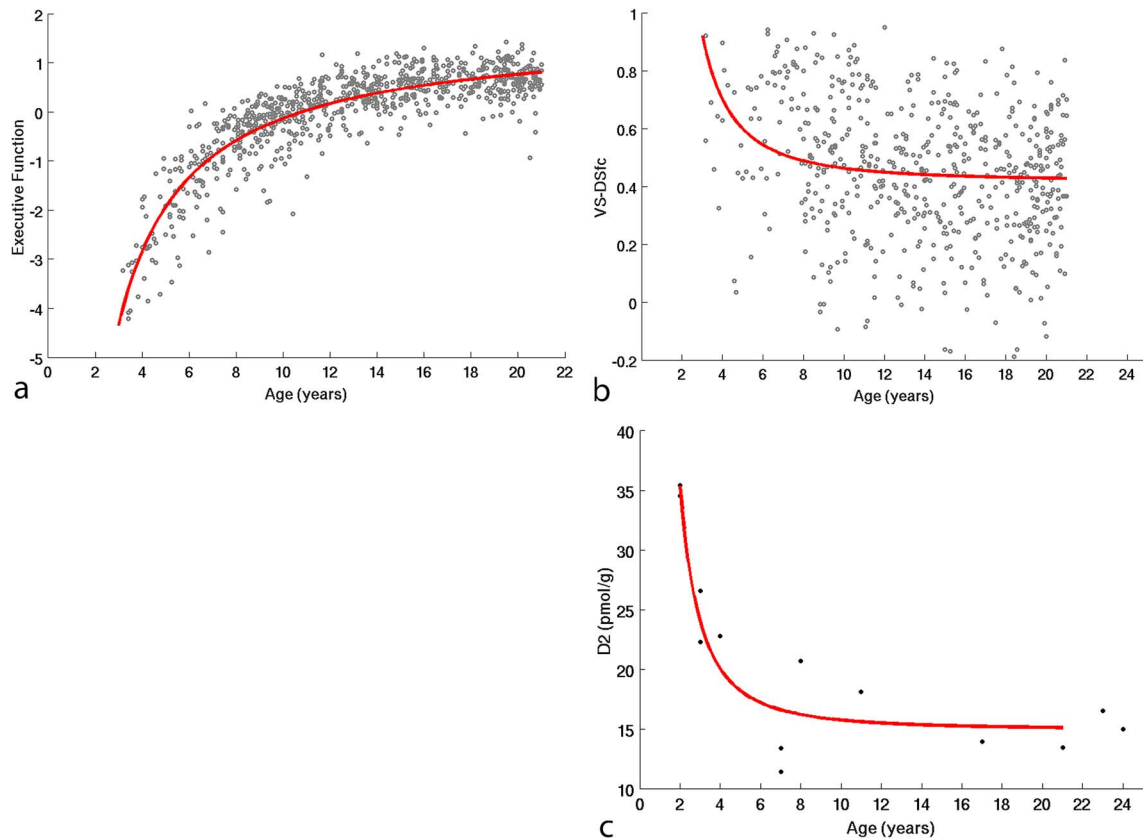


Figure 3. (a) The development of EF over age with a rapid increase in younger children followed by a slower increase toward asymptote. (b) VS-DS functional connectivity relation to age a derivative function of inverse age, showing a rapid decrease followed by a slower decrease and VS-DS_{fc} over age. (c) Derivative function of inverse age fitting the development of D2-receptor density in striatum based on the values reported in postmortem study (Seeman et al. 1987).

in the recent literature, which suggests substantial changes in structural and functional networks related to EF across developmental stages (Luna et al. 2015). From childhood to adolescence, there is increased integration between fronto-parietal regions (Hwang et al. 2013; Simmonds et al. 2014), which are related to top-down cognitive control and EF (Luna et al. 2004). These are in agreement with our results of positive effect of age on fronto-parietal connectivity and on EF.

In a separate analysis, we found that development of EF was best described by an inverse function, with a rapid increase in younger children followed by a gradually slower increase toward asymptote. (This model would of course only be applicable to development, not the decline during aging.) Interestingly, striatal connectivity was related to age as the derivative of that function, with a rapid decrease followed by a slower decrease (Fig. 3b). Note that our measure of striatal connectivity is the correlation between ventral and dorsal striatum, so it could reflect how VS affects DS via spiraling connections (Choi et al. 2012). Such connections include divergent projections from VTA or SN to ventral and dorsal striatum. We cannot exclude that such divergent projections were the only source of connectivity, that is, that the ventral-dorsal correlation reflected a co-activation by the VTA/SN, rather than originating in output from the VS. But both scenarios reflect striatal connectivity in that they involve activation of both VTA/SN, ventral and dorsal striatum, and are dependent on dopamine D2-receptors.

Development of D2-receptor density in striatum has previously been investigated in postmortem brains (Seeman et al.

1987). They reported a peak density at age 2, followed by a gradually slower decline (Fig. 3c), consistent with later imaging (Rinne et al. 1990). This is a very similar pattern to the decline of striatal connectivity that we found here, and can be significantly fitted by the same model (inverse of age squared). This suggests that the ventral-dorsal correlation in activity is closely related to D2-receptor density; consistent with the positive effect of D2-agonist on ventral-dorsal correlation (Piray et al. 2017), and in accordance with striatum's histology (Haber et al. 2000).

Thus it seems that striatal connectivity was related to the rate of cognitive improvement over time rather than absolute level of cognitive performance. In other words, the striatum might be more related to cognitive plasticity than capacity, as previously suggested (Klingberg 2014; Klingberg 2016). This is consistent with findings that striatal signal predicts future cognitive capacity (Ullman et al. 2014; Darki and Klingberg 2015; Nemmi et al. 2018), and is related to cognitive improvement during WM training (Olesen et al. 2004; Dahlin et al. 2008; Kuhn et al. 2013). The volume of the nucleus accumbens has previously been associated with a special kind of motivation called “grit” and positively associated with improvement during mathematical and WM training (Nemmi et al. 2016).

A role in cognitive plasticity is consistent with the role of striatum for learning (Knowlton and Squire 1993; Graybiel 2008). In psychological terms, it extends the role from learning of habits and implicit memory to include learning of cognitive functions. In neural terms, the same mechanisms might underlie some or all of these phenomena, namely a strengthening of

cortico-cortical connections. Since most parts of cortex connect to the striatum, the region of fronto-parietal convergence would presumably only be one of many convergence regions, affecting many networks.

We believe it is important to spell out the major limitations of the current study. First, our results are based on correlations of inter-individual differences, so, of course, are only indirect evidence of causation. In addition, our models were not able to discern the directionality of the effect between the striatal functional connectivity ($VS-DS_{fc}$) and fronto-parietal functional connectivity ($F-P_{fc}$). Although, as mentioned above on spiraling connections and striatal plasticity, we believe the striatum is driving the changes in fronto-parietal (which in turn drive improvements in EF). However, it could be the other way around with fronto-parietal being the driver.

Moreover, resting state functional connectivity analysis cannot distinguish between the direct and indirect functional connections. We only describe the relationship between connectivities with 1 observation per subject, not how 1 network affects the other on a second-by-second timeframe. In other words, the plasticity processes we are studying here are assumed to happen in a large time scale, where changes in striatal functional connectivity slowly change fronto-parietal connectivity over months or years. This is why we believe details on the time-series are less relevant to this study. The rs-fMRI data that we included in this study varied in the number of volumes due to different scanning time and motion scrubbing across subjects. Although we have controlled for this variable in the statistical analysis, this can be mentioned as one of the limitations. DTI and tractography methods are also sensitive to noise and motion that may lead to incomplete identification of structural connections. At last, our sample is cross-sectional, and so conclusions about age effects should be taken with caution.

Motivation, learning and EF have all been associated with striatal function. The present results are 1 step toward a model integrating these concepts where the connectivity between VS and convergence regions of the DS strengthens cortico-cortical connections. Exactly how this strengthening occurs, and for which other behavior this is relevant, will be a question for future research.

Notes

Data (Pediatric Imaging, Neurocognition, and Genetics Study (PING) data) used in the preparation of this manuscript were obtained and analyzed from the controlled access datasets distributed from the NIMH-supported Research Domain Criteria Database (RDoCdb). RDoCdb is a collaborative informatics system created by the National Institute of Mental Health to store and share data resulting from grants funded through the Research Domain Criteria (RDoC) project. *Conflict of Interest*: None declared.

Author Contributions

F.D., B.S., and T.K. conducted the analysis and wrote the paper.

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