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Permalink

<https://escholarship.org/uc/item/6926v1wg>

Journal

Biological Psychiatry Cognitive Neuroscience and Neuroimaging, 7(4)

ISSN

2451-9022

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Publication Date

2022-04-01

DOI

10.1016/j.bpsc.2021.05.002

Peer reviewed



HHS Public Access

Author manuscript

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2022 October 01.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2022 April ; 7(4): 415–423. doi:10.1016/j.bpsc.2021.05.002.

Limbic and Executive Meso- and Nigrostriatal Tracts Predict Impulsivity Differences in Attention-Deficit/Hyperactivity Disorder

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Abstract

BACKGROUND: Impulsivity is a defining characteristic of attention-deficit/hyperactivity disorder (ADHD), which has been associated with substance use disorders, higher accident rates, and lower educational and occupational outcomes. The meso- and nigrostriatal pathways of the dopamine system are hypothesized to be functionally heterogeneous, supporting diverse cognitive functions and impairments, including those associated with ADHD. We tested whether human midbrain pathways (where dopaminergic cell bodies originate) between the substantia nigra (SN) and ventral tegmental area (VTA) and the striatum differed between participants with ADHD and typically developing adolescent and young adult participants. We also assessed whether pathway connectivity predicted impulsivity regardless of diagnosis.

METHODS: Diffusion tensor imaging data were used to predict impulsivity (parent and self-report ratings, task-based behavioral measures) from participants with ADHD and typically developing adolescent and young adult participants ($n = 155$; 86 male, 69 female). Using probabilistic tractography, we mapped these pathways and divided the tracts into limbic,

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The authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.bpsc.2021.05.002>.

executive, and sensorimotor based on frontostriatal connectivity. ADHD and typically developing participants differed on all behavioral measures of impulsivity. We used correlation and machine learning analyses to test for a relationship between tract probabilities and impulsivity regardless of diagnosis.

RESULTS: Participants with ADHD had stronger structural connectivity between SN/VTA regions and the limbic striatum, weaker connectivity with the executive striatum, and no significant differences in sensorimotor tracts. Increased tract integrity between the limbic striatal and SN/VTA regions predicted greater impulsivity, while increased integrity between executive striatal and SN/VTA regions predicted reduced impulsivity.

CONCLUSIONS: These findings support the theory that functional diversity in the dopamine system is an important consideration for understanding dysfunction in ADHD.

In the context of attention-deficit/hyperactivity disorder (ADHD), impulsivity is associated with higher rates of suicidality and substance use disorders. ADHD has been linked to dysfunction of the dopamine system. Animal studies have shown that meso- and nigrostriatal pathways are functionally heterogeneous. We report that tracts between the human limbic and executive striatum and the substantia nigra (SN) and ventral tegmental area (VTA) differed between adolescent and young adult individuals with and without ADHD and also predicted impulsivity regardless of diagnosis. Increased limbic connectivity was associated with greater impulsivity; the inverse relationship was found for executive connectivity. These results comport with hypotheses that SN/VTA-striatal circuits provide a neurobiological pathway for affective signals to influence executive control, and ultimately behavior, including the negative outcomes associated with impulsivity, particularly in adolescents and young adults with ADHD.

Limbic and Executive Meso- and Nigrostriatal Tracts Predict Impulsivity in ADHD

Individuals with extreme impulsivity, such as in ADHD combined presentation, are noted for elevated levels of self-harm behaviors (e.g., suicide attempts) (1,2), gambling and substance use disorders (3,4), higher rates of accidents (5), and premature death (6). The worldwide annual economic burden associated with ADHD is in the hundreds of billions of dollars (7). Impulsivity is particularly concerning during adolescence and young adulthood, as choices during this period can have enduring consequences.

The dopamine system has long been implicated in impulsivity and ADHD (8), in addition to other cognitive functions and behavioral processes (9–12). The diversity of dopamine-dependent cognitive effects is presumed to derive from processes supported by efferent targets of dopamine neurons (13).

Connectivity between the frontal cortex and striatum is defined by heterogeneous corticostriatal loops that subserve sensorimotor, executive, and limbic functions. These loops are arranged in a dorsoventral configuration, with each structural loop maintaining the functional characteristics of the target cortical region (14–16). The striatum has been divided into limbic, executive, and motor subdivisions (17) based on frontal connectivity (18). These

subdivisions also likely reflect separable pathways from midbrain dopaminergic regions. The homogeneity of dopamine release measured with positron emission tomography in response to the administration of amphetamine (medication commonly used to treat ADHD) (19) is significantly higher within these functional subdivisions of the striatum compared to within anatomical subdivisions (i.e., putamen, caudate, and nucleus accumbens) (18).

Evidence for segregation in midbrain dopamine-related neuron pathways derives primarily from animal work. The primary anatomical subdivision within the SN/VTA divides neurons into dorsal and ventral tiers (20). The dorsal tier includes the VTA and the dorsal SN pars compacta (SNc), while the ventral tier includes the densocellular region and the cell columns that extend deep into the SN pars reticulata. Projections to the striatum have a medial/lateral and inverse ventral/dorsal topographical arrangement from the VTA, SNc, and SN pars reticulata (21–24). The sensorimotor and executive dorsal striatum receive inputs primarily from the ventral midbrain, and the ventral striatum (limbic) is innervated primarily by dorsal tier, the dorsal part of the ventral tier, and the dorsomedial SN pars reticulata (21,24–26). We used these findings as a priori predictions about the arrangement of tracts with end points in the human SN/VTA and striatum [c.f., (18)].

The anatomical subdivisions of the SN/VTA are hypothesized to retain the functional properties of their efferent projections. Limbic, executive, and motor functions are evident in the firing properties of neurons across functional subdivisions of SN/VTA. Single-unit recordings in animals have shown that cells in the VTA and medial SNc encode reward signals, characteristic of limbic processing. By contrast, neurons in more ventrolateral cells respond to salient events, which is expected for modulation of executive processes (27). Cells in the most ventrolateral regions of the SNc that innervate the sensorimotor putamen are crucial for motor control. A characteristic of Parkinson's disease is preferential loss of these cells (28).

Increased impulsivity, a central behavioral manifestation of ADHD, is proposed to derive from dopaminergic deficits (8) that produce an imbalance in limbic and executive control systems [e.g., (29)]. In this dual pathway model, the reward system drives impulses while the executive control system evaluates and regulates these impulses (30–33). Identification of SN/VTA-striatum tracts allowed us to test two hypotheses about the dual pathway model of ADHD: 1) that individuals with ADHD and typically developing (TD) individuals differ in the structural integrity of limbic and executive tracts and 2) that the integrity of the SN/VTA-striatum tracts differentially predicts impulsivity, regardless of diagnosis. We used diffusion tensor imaging (DTI) combined with probabilistic tractography to assess the connectivity of midbrain pathways consistent with the dopamine signaling system in adolescent and young adult participants by defining streamlines with end points in regions of the SN/VTA and the limbic, executive, or sensorimotor striatum (18).

METHODS AND MATERIALS

Participants

We recruited 160 adolescent and young adult participants, 5 of whom (1 participant with ADHD and 4 TD participants) were dropped from analyses for not having any successful

DTI streamlines reach to one or more striatal targets, leaving a final sample of 155 participants (12–24 years of age; mean age = 16.52 years, SD = 3.38 years). Of these, 74 were diagnosed with ADHD and significant impulsivity (50 male, 24 female). The remaining 81 were TD (36 male, 45 female). Detailed demographic information can be found in the Supplement. The number of subjects recruited for this study was determined by power calculations for a larger parent study examining the relationship between cognitive control, reward processing, and delay discounting in ADHD. This article is the result of a planned exploratory analysis.

Behavioral Measures of Impulsivity

Impulsivity was measured using surveys and task-based measures. Participants completed the adolescent or adult version of the Barratt Impulsiveness Scale depending on age (34). The parents of the participants completed either the Conners Adult ADHD Rating Scales–Observer or the Conners Parent Rating Scale. Adult participants also completed the Conners Adult ADHD Rating Scales–Self-Report for supplemental information. The Zimbardo Time Perspective Inventory was administered, and we were particularly interested in two factors—present hedonism and future orientation—that have been shown to be associated with impulsivity (35). Finally, participants completed a delay discounting task in which they made a series of choices between smaller, immediate and delayed, larger monetary rewards (36). The percentage of “smaller sooner” preferences was used as an index of impulsivity.

The differences in behavioral measures between the participants with ADHD and TD participants were assessed using separate independent-sample *t* tests with Bonferroni correction for multiple comparisons (Figure 1). Owing to the large number and diversity of behavioral assessments, impulsivity measures were aggregated into one latent factor using maximum likelihood factor analysis. Instead of principal component analysis, which extracts orthogonal components, we used maximum likelihood factor analysis, which accounts for covariance among variables. This method is more appropriate for estimating latent factors (37). Graphical examination of the scree plot using the scree test revealed one meaningful factor (Figure S1) (38). We interpreted the first factor as a latent construct representing impulsivity (see the Supplement for additional details). We used this factor score as our measure of impulsivity for correlational analyses with tract strength measures.

Magnetic Resonance Imaging Preprocessing and Analysis

Diffusion-Weighted Magnetic Resonance Imaging.—Diffusion-weighted data were processed using the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). Measures of tract strength were calculated using probabilistic tractography (39,40). Because previous studies have shown that the structural integrity of specific subsets of striatal tracts is related to different components of behavior (41,42), the goal of our structural connectivity analysis was to identify and quantify specific tracts with end points in the SN/VTA and striatum (limbic, executive, and motor regions). Because the dorsal and ventral tiers of the SN and VTA have not yet been resolved in humans with magnetic resonance imaging, we use the term “SN/VTA-striatum tracts” to describe meso- and nigrostriatal tracts. The use of this term is not meant to imply directionality, because diffusion-weighted imaging data do not include information about whether tracts are efferent or afferent. We tested whether the

SN/VTA-striatum tracts differed among the participants with ADHD and TD participants. We also related integrity measures of these tracts to individual differences in impulsivity.

Fiber tracking was conducted in parallel for each voxel within a predefined SN/VTA seed mask. Target areas in the striatum were defined using a connectivity-based segmentation atlas with subdivisions for limbic, executive, and sensorimotor regions available in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases/striatumconn>). Because amphetamine-induced dopamine release measured with positron emission tomography is significantly more homogeneous when the striatum is functionally parcellated based on cortical targets instead of anatomical regions like caudate, putamen, and nucleus accumbens, we used function-based regions of interest (ROIs) based on Tziortzi *et al.* (18). The seed ROI for the SN/VTA was defined using a probabilistic atlas of human SN/VTA (Figure 2) (43).

Tractography was performed separately for the left and right striatum, and possible tracts were restricted to the hemisphere of origin using an exclusion mask of the contralateral hemisphere. This resulted in six value maps per participant, one for each target region and each hemisphere (3 striatal regions \times 2 hemispheres). We used the mean of these value maps as the measure of SN/VTA-striatum tract strength.

To determine how the SN/VTA-striatum tracts were organized across participants, individual probability maps were normalized into Montreal Neurological Institute space. Each map was then thresholded so that only voxels that had at least 50 samples reaching any target region were included. The resulting maps were averaged to create six value maps for the entire sample of participants (Figure 3). A detailed description of the imaging acquisition, procedure, and analysis can be found in the Supplement.

Tract Strength Differences Between Participants With ADHD and TD

Participants.—To test for differences in tract strength between the participants with ADHD and TD participants, we calculated the mean of the tract probability within each individually determined SN/VTA-striatum segment (three per hemisphere, six in total). We used multivariate analysis of covariance for this calculation. Age and intracranial volume were included as covariates. The six tract strength measures were the dependent variables, and a positive ADHD diagnosis was the independent variable.

The ultimate goal of cognitive neuroscience is to be able to predict important aspects of behavior from brain structure and function. Prediction is difficult with generalized linear model approaches due to well-known overfitting problems. Therefore, machine learning (i.e., least absolute shrinkage and selection operator [LASSO] regression) (44) was used to predict ADHD diagnosis from the six SN/VTA-striatum tract strength measures. We used LASSO instead of other possible techniques because it is well suited to magnetic resonance imaging data (45). The measures were controlled for age and intracranial volume by regressing each measure (impulsivity, motor, executive, and limbic tract strength in each hemisphere) onto age and intracranial volume. The residuals from the seven regressions were used for the LASSO regression. We implemented a leave-one-subject-out cross-validation loop (46) in R version 3.6.2 (R Foundation for Statistical Computing) with the *glmnet* package using a binomial response type for the binary dependent variable

(i.e., positive ADHD diagnosis) (47). Mean LASSO regression coefficients and confidence intervals (CIs) were calculated as the mean of the coefficients across each of the leave-one-out fits (i.e., jackknife resampling). Coefficients were considered significantly different from zero if the 95% CIs did not contain zero.

Tract Strength and Impulsivity.—In addition to testing for tract strength differences categorically (between participants with ADHD and TD participants), we also tested where tract strength measures were correlated with behavioral measures of impulsivity regardless of diagnosis. There is increasing effort to consider disorders like ADHD to be reflective of extremes of a continuous underlying cognitive difference (e.g., impulsivity). To test whether individual differences in impulsivity were related to SN/VTA-striatum tract strength, Spearman's rank-order correlations were calculated between tract strength measures and the behavioral factor score of impulsivity (the tract strength values are not normally distributed, so nonparametric correlations are appropriate) (Figure 4). Age and intracranial volume were included as covariates. Bonferroni correction was applied for all six comparisons (3 targets \times 2 hemispheres). Results were considered statistically significant if they were less than the Bonferroni corrected value of .008. Machine learning (i.e., LASSO regression) (44) was used to predict impulsivity from the six SN/VTA-striatum tract strength measures. This analysis mirrored the LASSO regression predicting ADHD diagnosis, except that the model now implemented a Gaussian response type for the continuous dependent variable.

RESULTS

Participants with ADHD and TD participants differed across all behavioral and rating scale measures of impulsivity (Figure 1, Table 1); thus, we calculated an aggregate impulsivity score using maximum likelihood factor analysis to extract the shared variance among the behavioral measures. Table 2 displays the factor loadings and communalities for each of the six behavioral measures. One primary factor emerged that had an eigenvalue of 2.84 and explained 47.40% of the variance. All measures that correlated positively with impulsivity had positive factor loadings, and the one measure that correlated negatively with impulsivity (Zimbardo Time Perspective Inventory future orientation) had a negative factor loading, as expected. We interpreted this factor to represent impulsivity, with greater scores reflecting more impulsive decision making, and used the factor score for further analysis.

Functional Organization of the SN/VTA

When tracts with end points in the midbrain SN/VTA and functionally parcellated striatal regions were classified, three subdivisions emerged within the midbrain SN/VTA (Figure 3). The organization of these subdivisions was consistent with known anatomy in nonhuman primates (13).

We performed two parallel analyses to test for differences in SN/VTA-striatum tracts based on group (ADHD vs. TD) and based on a continuous relationship with our aggregate measure of impulsivity. These analyses are not independent, but instead are separate ways to test for differences in SN/VTA-striatum connectivity related to ADHD. We conducted the two parallel sets of analyses for completeness.

First, to test for group differences in tract strength between the participants with ADHD and TD participants, we calculated the mean of the tract probabilities within each individually determined SN/VTA-striatum tract segment (three per hemisphere, six in total). We implemented multivariate analysis of covariance, with age and intracranial volume as covariates, the six tract strength measures as dependent variables, and a positive ADHD diagnosis as the independent variable. When controlling for age and intracranial volume, the executive and limbic SN/VTA-striatum tract strength measures differed between participants with ADHD and TD participants, albeit in opposite directions (Table 3). In the right hemisphere, participants with ADHD had greater structural connectivity in the limbic SN/VTA-striatum tract compared with TD participants ($F_{1,154} = 8.860$, $p < .01$ Bonferroni corrected, $\eta_p^2 = 0.056$) but decreased structural connectivity in the executive tract ($F_{1,154} = 4.292$, $p < .05$ Bonferroni corrected, $\eta_p^2 = 0.028$). This difference was only significant in the right hemisphere. No differences were found in sensorimotor tracts across the two groups (Table 3).

To test whether tract strength predicted ADHD diagnosis, we used machine learning techniques (binomial LASSO) to predict ADHD diagnosis in individual subjects. The leave-one-subject-out cross-validation analysis showed that SN/VTA-striatum tract strengths measures significantly predicted ADHD diagnosis (Spearman's $\rho = 0.22$, $p < .01$, 2-tailed). We calculated 95% CIs on the LASSO regression coefficients using jackknife resampling. CIs did not include zero only for the right limbic ($\beta = 0.21$; 95% CI, 0.14 to 0.27) and right executive ($\beta = -0.17$; 95% CI, -0.23 to -0.08) tracts.

ADHD may be considered an extreme of variation in a behavioral phenotype presenting on a continuum that varies dimensionally across all people. One candidate behavioral measure that may partially define ADHD is impulsivity. We conducted a second set of analyses to determine whether individual differences in impulsivity were related to SN/VTA-striatum tract strength, regardless of diagnosis. We computed Spearman's rank-order correlations between the tract strength measures and aggregate impulsivity score. Age and intracranial volume were included as covariates. Individual differences in impulsivity were negatively associated with tract strength between the SN/VTA and executive striatum (Spearman's $\rho = -0.23$, $p < .05$, Bonferroni corrected). Conversely, individual differences in impulsivity were positively associated with tract strength between the SN/VTA and limbic striatum (Spearman's $\rho = 0.22$, $p < .05$, Bonferroni corrected). These results were again significant in the right hemisphere only.

While the correlations revealed distinct relationships between SN/VTA-striatum tracts and impulsivity, correlations lack predictive power. To resolve this, we used LASSO to predict impulsivity in individual subjects. The results from the leave-one-subject-out cross-validation analysis revealed that SN/VTA-striatum tract strength measures significantly predict impulsivity (Spearman's $\rho = 0.17$, $p < .05$, 2-tailed). We calculated 95% CIs on the LASSO regression coefficients using jackknife resampling. CIs did not include zero only for the right limbic ($\beta = 0.07$; 95% CI, 0.05 to 0.10) and right executive ($\beta = -0.13$; 95% CI, -0.16 to -0.11) tracts.

Overall, our results suggest that strength of limbic SN/VTA-striatum tracts in the participants with ADHD was greater than in the TD group, and executive SN/VTA-striatum tracts in the participants with ADHD were less than in the TD group. The strengths of these tracts were predictive of impulsivity, suggesting that observed anatomical differences contribute to the observed differences in impulsivity between the ADHD and TD groups.

DISCUSSION

The dopamine system has long been implicated in impulsivity and ADHD [e.g., (48,49)]. This association derives in large part from the fact that stimulant medications selective for dopamine receptors are effective and commonly used treatments for ADHD (50). Data also show that dopamine agonists acutely increase impulsivity (51). However, details about how the dopamine system relates to impulsivity and symptoms of ADHD is still actively being investigated. This study provides a new contribution to this field, demonstrating that dopamine-related limbic and executive tracts from midbrain nuclei (SN/VTA) differentially predict impulsivity and ADHD.

The anatomy of human midbrain neurons and their afferent and efferent projections remains understudied. Confirmation of connectivity patterns requires study of postmortem tissue. However, anatomy in nonhuman primates indicates that dopamine neurons can be partitioned into dorsal and ventral tiers based on cell morphology and connectivity patterns (26,52). There is an overall connectivity pattern such that medial regions of SN/VTA are interconnected with ventral regions of striatum. This pattern of connectivity was shown in our tractography using DTI, giving us confidence in the projection patterns estimated in our dataset. However, it is important to note that human DTI is too coarse-grained of a technique to distinguish dopaminergic SN/VTA projections from other proximal, and often intermingled, pathways.

The functional organization of SN/VTA neurons has been argued to derive from striatal connectivity, which in turn depends on corticostriatal connectivity (13). We characterized the organization of the human midbrain SN/VTA in terms of its connections to limbic, executive, and motor striatal regions (18). It is unclear whether these are appropriate categorical subdivisions, or whether the striatum includes more or even continuous distributions of function. The limbic, executive, and motor distinctions fit with common distinctions of frontal cortex function [e.g., (53)] and have been shown to have greater homogeneity of dopamine release than structural subdivisions (18). We feel that this separation of functions is a reasonable current approximation and may be particularly appropriate when considering relationships between brain networks and behavior such as impulsivity. Impulsivity has long been believed to depend on interactions between affective drive (limbic) and controlled regulation of those drives (executive) (54,55).

We used these tract integrity measures to test whether connections of the limbic and executive striatal circuits to SN/VTA regions differed between individuals with ADHD and TD control subjects. Compared with the control group, the ADHD group had lower tract integrity values between SN/VTA and executive striatum. They also had greater tract integrity values between SN/VTA and limbic striatum. The tract integrity values

associated with tracts connecting the executive and limbic striatum with midbrain SN/VTA regions were also predictive of individual differences in impulsivity. Individuals with higher connectivity in the executive circuit had lower impulsivity scores. Conversely, individuals with higher connectivity in the limbic circuit had higher impulsivity scores. These results are in line with hypotheses that the spiraling SN/VTA-striatum circuits provide a neurobiological pathway for affective signals to influence executive control signals and ultimately behavior (13). They also support the Research Domain Criteria framework that clinically important phenotypes such as impulsivity may exist on a spectrum with common biological substrates, and that clinical diagnoses like ADHD reflect extremes of these phenotypes.

Previous studies have used DTI to show that corticostriatal circuits are differentially related to impulsivity (35,42,56). It is intriguing to consider that the true physiological basis of impulsivity may be large-scale networks that span numerous brain regions. This would fit with findings from whole-brain functional connectivity analyses showing long-range networks (57). It remains a future objective to determine the full extent of brain networks related to impulsivity. Relatedly, we conducted exploratory meditation analyses to determine whether tract strength accounted for the relationship between ADHD and impulsivity. These analyses were not significant and were not reported in the Results. We suspect that ADHD and impulsivity is mediated by brain connectivity but that the SN/VTA-striatum tracts that we studied are only a part of the patterns of connectivity that underlie this relationship.

Our study found significant effects between SN/VTA-striatum connectivity and impulsivity in the right hemisphere only. Although we did not have a priori hypotheses regarding lateralization of effects, previous studies have also found significant effects in only the right hemisphere of the brain in studies of ADHD (58–60). Some researchers have hypothesized that ADHD is primarily a right hemisphere syndrome (61) or is an imbalance between right and left hemispheres (62). The localization of effects to the right hemisphere in this study are consistent with this lateralization hypothesis.

In addition to striatal regions, midbrain dopamine neurons have diverse projections to frontal, parietal, occipital, and temporal cortices (63,64). Midbrain dopamine neurons also project to many midline structures such as the hippocampus, amygdala, hypothalamus, and periaqueductal gray. These projections might have functionally distinct roles in regulating a plethora of cognitive functions (for example, the VTA-hippocampal circuit is hypothesized to control the encoding of information into long-term memory) (10,65,66). We expect that other cognitive processes with known dependence on dopamine function specifically depend on some of these other projection pathways.

One limitation of this study is that a subset of the ADHD group included participants with a history of medication prescribed for their ADHD. Although participants were free of ADHD medication for five half-lives before the imaging data were acquired, the effects of prior medication use are unknown. Given that stimulant medication in individuals with ADHD has been shown to reduce behavioral symptomatology and might be associated with normalization of brain structure abnormalities (67), the heterogeneity in medication history

could have affected the findings or added noise to the results. The addition of a drug-naïve group would mitigate this concern but is challenging in practice.

Although participants were excluded from the study if they did not achieve a Full Scale IQ score >80 (see the Supplement for more information), an independent-samples *t* test revealed a significant difference in IQ scores between participants with ADHD (mean = 106.68, SD = 13.22) and TD participants (mean = 114.67, SD = 11.34) ($t_{150} = -4.01$, $p < .001$, Cohen's $d = 12.26$ [3 participants with ADHD were missing scores]). Although differences in IQ have been previously observed in the literature (68), this observed difference is a limitation in the current study.

Another limitation is potential sex differences between groups. Although the current study aimed to recruit close to an equal number of males and females per group as possible, this is difficult in practice given that males are about three times more likely to be diagnosed with ADHD than females (69). Our sample included 68% males in the ADHD group and 44% males in the TD group. This is an area of growing interest, as there are known differences in ADHD symptoms between males and females as well (e.g., males typically show externalized symptoms, whereas females show internalized symptoms) (70). Future research should investigate neuroanatomical differences related to sex in ADHD.

Impulsivity is a central component of ADHD but does not capture the full manifestation of the disorder. We took these issues into account in developing the inclusion and exclusion criteria and during the subject recruitment and evaluation process to mitigate potential confounding clinical differences. Additionally, we acknowledge that impulsivity may be an aggregate construct [e.g., (71)] with multiple underlying behavioral and neural constructs. Our data indicate that a single factor best described variability across participants on our numerous measures. We also note that impulsivity is a common focus for the etiology of ADHD. Even if a construct different from impulsivity truly defined ADHD, or if a subcomponent of impulsivity is most relevant to ADHD, we believe that our results contribute significantly to understanding of the disorder.

This work provides novel insight into the architecture of connections between the dopamine-related human midbrain pathways and striatum. The strength of the connections between the limbic and executive striatum and midbrain SN/VTA differed between the ADHD and TD groups and also predicted individual differences in impulsive behavior. These results provide evidence for differential neuroanatomical circuits that manifest impulsive behavior and ADHD symptomatology. Neuroimaging techniques could potentially be used in the future to identify neuroanatomical subtypes of ADHD. Because previous studies have shown that the reward system develops earlier than the executive control system (32,72–75), investigating the neuroanatomy of this system across development as it relates to ADHD symptomatology will be an exciting future direction of research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Science Foundation Graduate Research Fellowships Program (to BLE), National Science Foundation Grant No. 1634179 (to SMM), and National Institute of Mental Health Grant No. 2 R01 MH091068 (to JBS and SMM).

The authors thank J. Faye Dixon, Ph.D., for assistance with the diagnostic procedure and Murat Pakyurek for screening for medical concerns. The authors acknowledge the kind support of all their research participants, as well as of Catherine Fassbender, Ph.D.; Tadeus Arthur Hartanto, M.B.A.; Catrina A. Calub, M.A.; Amrita Ramakrishnan; Erin Calfee, M.A.; Lauren Boyle, Ph.D.; Laurel Cavallo; Maria B.E. Menor; Jessica Nguyen; and Steven J. Riley, M.A.

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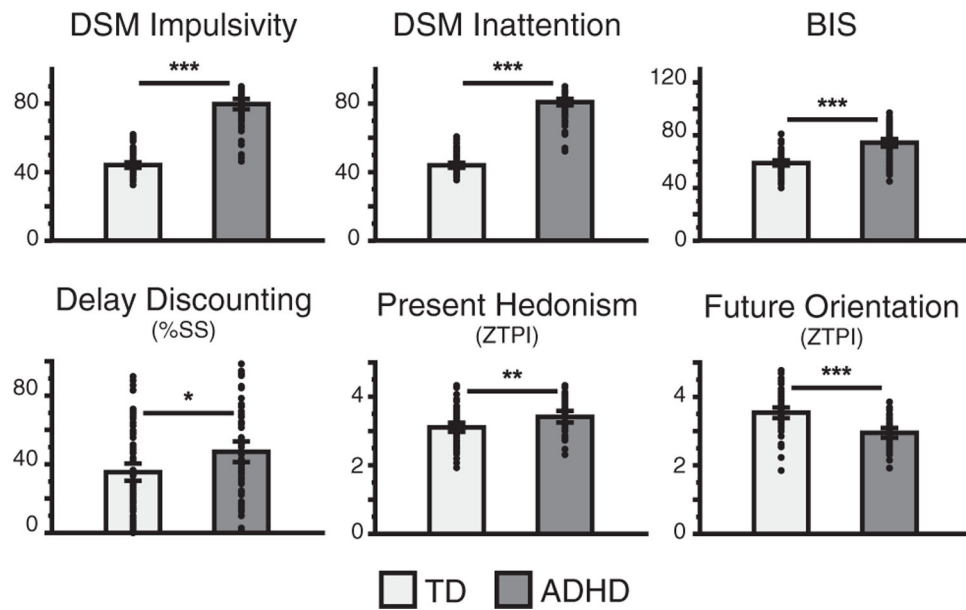


Figure 1. Behavioral measures of impulsivity for participants with attention-deficit/hyperactivity disorder (ADHD) and typically developing (TD) participants. Individual points are subjects. Error bars represent 95% confidence interval. * $p < .05$, ** $p < .01$, *** $p < .001$. %SS, percent of smaller sooner choices; BIS, Barratt Impulsiveness Scale; ZTPI, Zimbardo Time Perspective Inventory.

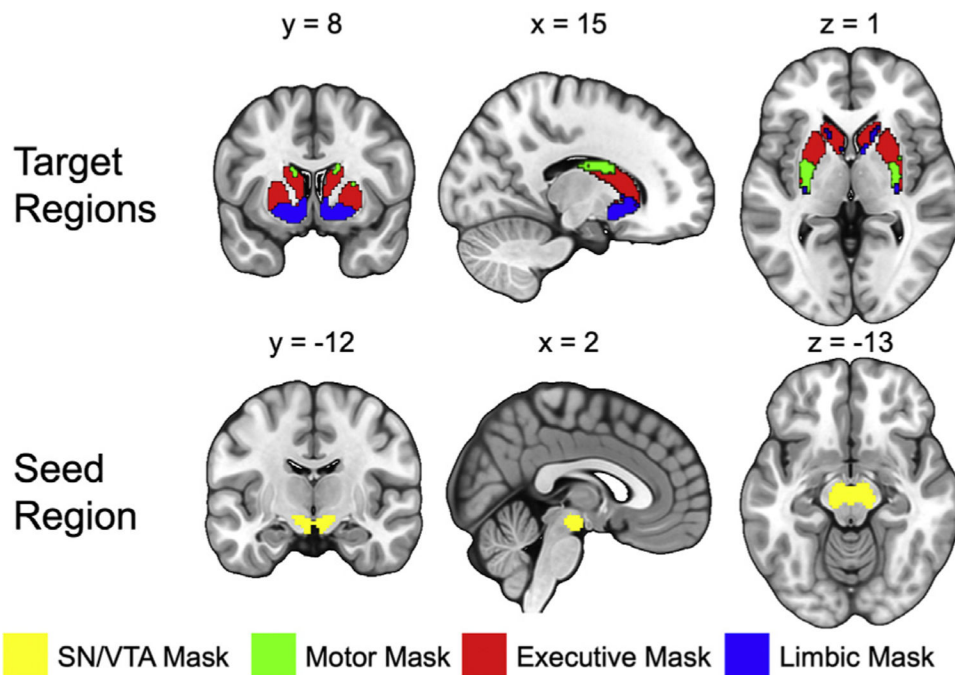


Figure 2.

Seed region and target regions for the tractography analysis. The target regions of the striatum were functionally segmented based on projections to motor, executive, and limbic cortices [from Tziortzi *et al.* (18)]. The seed region of the midbrain was generated from a probabilistic substantia nigra (SN)/ventral tegmental area (VTA) mask [from Murty *et al.* (43)]. The probabilistic mask was thresholded at 50% and binarized to create the seed mask for tractography analysis. These masks were then tailored to each subject's T1-weighted anatomical scan.

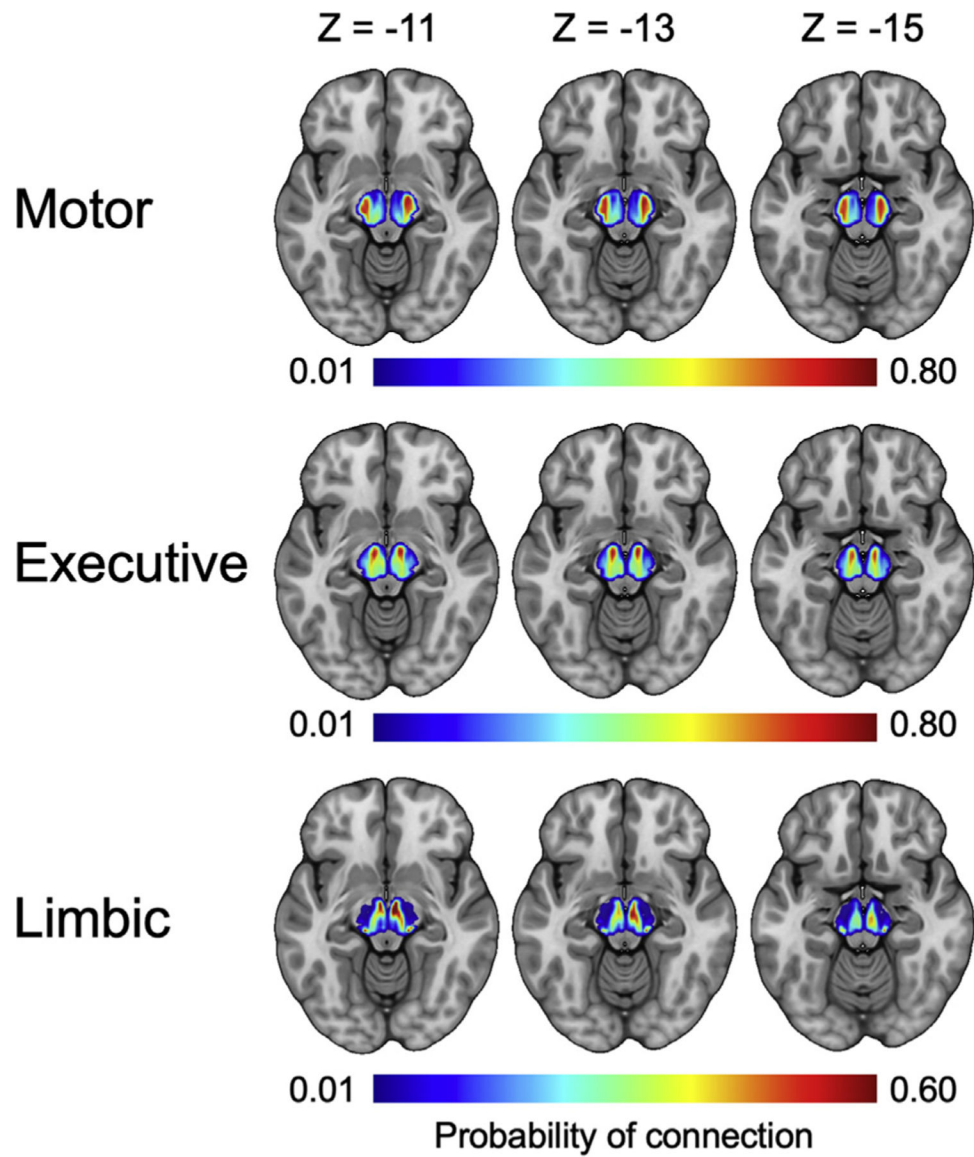


Figure 3. Group average projections from the three functional striatum targets (motor, executive, limbic) to the substantia nigra/ventral tegmental area. Each column corresponds to a different axial plane. A threshold of 50 samples was applied to each participant's image prior to averaging.

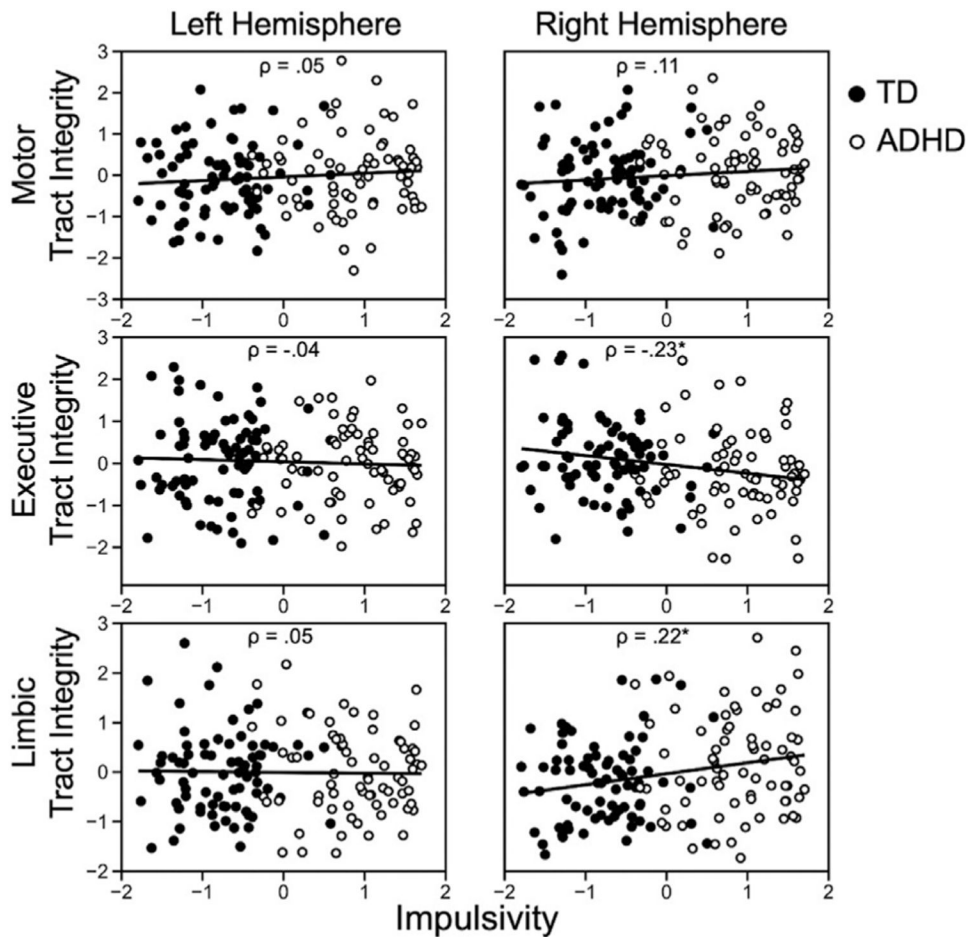


Figure 4. Spearman's rank-order correlations between impulsivity and substantia nigra/ventral tegmental area-striatum tract strength measure from the three functional striatum targets (motor, executive, limbic), controlling for age and intracranial volume. ADHD, attention-deficit/hyperactivity disorder; TD, typically developing.

Table 1. Descriptive Statistics and Independent-Samples t Tests for the Behavioral Measures

Behavioral Measure	ADHD Group		TD Group		<i>t</i>	<i>df</i>	Cohen's <i>d</i>
	Mean	SD	Mean	SD			
DSM Impulsivity	79.66	12.45	43.95	7.07	21.45 ^a	142	3.53
DSM Inattention	80.83	9.53	43.81	6.35	27.68 ^a	142	4.57
BIS	74.27	11.82	58.68	8.45	9.26 ^a	144	1.52
Delay Discounting	47.26	27.06	35.70	24.04	2.82 ^b	153	0.45
Present Hedonism	3.42	0.54	3.10	0.53	2.95 ^b	101	0.60
Future Orientation	2.95	0.46	3.54	0.61	-5.36 ^a	101	1.09

DSM impulsivity and DSM inattention are derived from the Conners Adult ADHD Rating Scale or Conners Parent Rating Scale or Conners Adult ADHD Rating Scales subscales. Delay discounting is derived from the percent of smaller sooner choices. Present hedonism is derived from the Zimbardo Time Perspective Inventory present hedonism, and future orientation is derived from the Zimbardo Time Perspective Inventory future orientation. Differences in degrees of freedom across measures reflect missing data.

ADHD, attention-deficit/hyperactivity disorder; BIS, Barratt Impulsiveness Scale; TD, typically developing.

^a $p < .001$.

^b $p < .01$.

Table 2. Factor Loadings and Communalities Based on Maximum Likelihood Estimation Factor Analysis

	Impulsivity (Factor 1)	Factor 2	Communality
DSM Impulsivity	0.909	0.034	0.817
DSM Inattention	0.991	-0.021	0.831
BIS	0.599	0.287	0.422
Delay Discounting	0.145	-0.167	0.061
Present Hedonism	0.255	0.787	0.215
Future Orientation	-0.422	-0.325	0.258

DSM impulsivity and DSM inattention are derived from the Conners Adult ADHD Rating Scale or Conners Adult ADHD Rating Scales subscales. Delay discounting is derived from the percent of smaller sooner choices. Present hedonism is derived from the Zimbardo Time Perspective Inventory present hedonism, and future orientation is derived from the Zimbardo Time Perspective Inventory future orientation. Differences in degrees of freedom across measures reflect missing data.

ADHD, attention-deficit/hyperactivity disorder; BIS, Barratt Impulsiveness Scale.

Table 3.
Group Comparisons of Tract Integrity Controlling for Age and Intracranial Volume

	TD		ADHD		Difference (TD-ADHD)	F	Partial η^2
	EMM	SEM	EMM	SEM			
Left Motor	0.429	0.010	0.439	0.011	-0.011	0.473	0.003
Left Executive	0.470	0.011	0.457	0.012	0.013	0.592	0.004
Left Limbic	0.139	0.008	0.145	0.009	-0.006	0.234	0.002
Right Motor	0.443	0.009	0.455	0.009	-0.012	0.837	0.006
Right Executive	0.444	0.010	0.414	0.010	0.030 ^a	4.292	0.028
Right Limbic	0.165	0.007	0.196	0.007	-0.031 ^b	8.860	0.056

ADHD, attention-deficit/hyperactivity disorder; EMM, estimated marginal mean; SEM, standard error of the mean; TD, typically developing.

^a $p < .01$ (Bonferroni corrected).

^b $p < .001$ (Bonferroni corrected).