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

Supplemental Information

Supplemental Methods

Participants. We recruited 160 AYA participants, 5 of whom (1 ADHD and 4 TD) were dropped from analyses for not having any successful DTI streamlines reach to one or more striatal target, leaving a final sample of 155 participants (aged 12-24 years, 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 typically developing (TD; 36 male, 45 female). The participants were recruited from psychiatric and neurodevelopmental disorders clinics, a university-based institute subject recruitment system, and the community via targeted advertising on flyers and social media.

Socioeconomic Status. Socioeconomic status (SES) was determined based on educational attainment and income. Adult participants reported on their income and educational level. Most adults diagnosed with ADHD reported some college (70.0%), 10.0% reported having completed an Associate's degree, and the remaining participants (20%) having completed a Bachelor's degree. Of the adults included in the TD group, 33.3% reported having graduated high school or some college, whereas 57.6% reported an Associate's or Bachelor's degree, 3.0% reported a Master's degree, and 6.0% reported a professional or doctoral degree. For income, 77.8% of adults in the ADHD group reported earning up to $25,000, 11.1 % reported an annual income of up to $50,000, and 11.1% reported an income of over $50,000 (with one participant missing income data). Similarly, 61.3%% of adults in the TD group reported an annual income of up to $25,000,

19.4% reported earning up to $50,000, 12.9% reported earning up to $75,000, and 6.5% reported earning over $100,000 (with two participants missing income data). For minors, SES was based on parental report of their own educational attainment and income as well as of their partners, if applicable. Approximately 22.6% of parents of children in the ADHD group reported some college, 16.4% reported an Associate's degree, 30.6% reported a Bachelor's degree; 14.5% reported a Master's degree, and 16.4% reported a professional or Doctoral degree. For the TD group, 2.1% of parents reported some K-12 education, 12.5% reported having graduated high school or some college, 18.75% reported an Associates, 35.4% reported a Bachelor's degree; 16.7% reported a Master's degree, and 14.6% reported a Doctoral degree or a professional degree. Household income was estimated by summing the lower and upper ends of categorical values provided by parents regarding theirs and their partner income, if applicable. Many parents in both the ADHD and TD groups reported a household income of over $100, 000 (ADHD= 55%; TD= 38.3%); 33.3 % of the ADHD and 46.8% of the TD group fell within the $50,000-$125,000 range, and 11.67% of the ADHD and 14.9% of the TD groups reported earning between $0-$50,000 (2 ADHD participants and 1 TD participant were missing income data).

Diagnostic Procedures. Two licensed psychologists on our team (JBS and JFD) evaluated phone screen data to assess eligibility for the study based on the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM 5). Volunteers passing the phone screen were invited for an in-person comprehensive psychiatric evaluation. All participants in both the TD and ADHD completed all evaluation procedures. Volunteers needed to meet criteria for either the ADHD, Combined Presentation, with clinically significant symptoms of hyperactive/impulsive and inattentive behavior or the ADHD, Hyperactive/Impulsive Presentation, with symptoms primarily in the hyperactive/impulsive domain. Hyperactive and impulsive symptoms load on the same

factor in previous diagnostic procedures (1). Participants and their parents (or spouses, partners in adults for current behavior) participated in a structured clinical interview (Diagnostic Interview Schedule for Child and Adolescents and the Young Adult version for the adults; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) or the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid) – 5 (2) or the MINI – 5 for adults (3) assessing for ADHD, typical development, and the presence of any other major psychiatric disorder (oppositional defiant disorder, conduct disorder, phobia, obsessive compulsive disorder, panic disorder, major depression, bipolar disorder, psychosis, anxiety disorders, substance use disorder, anti-social personality, and post-traumatic stress disorder). To further assess for ADHD we collected rating scale data on current ADHD symptoms from parents [Conner-3 Parent Rating Scale - CPRS-3; (4)] and in the adolescents, teachers (Conners-3 Teacher Rating Scale - CTRS-3), whereas the adult participants had the Conners' Adult ADHD Rating Scale [CAARS; (5)] with parent, spouse or close friend (these were primarily completed by parents) completing the Observer form of the CAARS on the participant, with T-scores of 65 or greater considered clinically significant. Childhood presence of ADHD for adult ADHD participants was also confirmed (or absence for TD) via retrospective rating scales completed by parents on the Barkley Adult ADHD Rating Scale--IV [BAARS-IV; (6)]. In accordance with the DSM, participants in the ADHD group needed to exhibit a persistent pattern of clinically significant level of hyperactive/impulsive symptoms and impairment in the home and school or work setting and before 12 years of age, with the symptoms not better explained by another mental disorder. Participants also underwent an assessment of intellectual and academic functioning (see below). The diagnostic process was completed using best practice recommendations (7), with a licensed psychologist reviewing all of

the diagnostic information to determine whether or not volunteers met criteria for ADHD, TD, or the presence of another psychiatric disorder.

Study Inclusion/Exclusion Criteria. Study inclusion criteria required participants to be between the ages of 12 and 24 years of age, be typically developing for the TD group or meet DSM-5 criteria for ADHD, Combined or Hyperactive/Impulsive Presentation for the ADHD group. (All participants in this study ADHD group met criteria for the Combined presentation; none for the Hyperactive/Impulsive Presentation.) Study exclusion criteria included (a) Full Scale IQ score < 80 [full scale IQ score was based on the Wechsler Intelligence Scale for Children (WISC-IV); (8)] or the Wechsler Adult Intelligence Scale [WAIS; (9)], depending on age; (b) testing positive for a mathematical or reading learning disability [Wechsler Individual Achievement Test–Third Edition, WIAT-III, scores < 80; (10)]; (c) any parent-reported history of head trauma, neurological disorder or major medical problem; (d) prescribed psychoactive medication besides ADHD medications (i.e., stimulants or atomoxetine); (e) meeting DSM criteria for any other Axis I diagnosis besides ADHD, oppositional defiant disorder, or conduct disorder; (f) a positive drug screen on the day of the imaging session for illicit drugs; (g) a positive pregnancy test (female); (h) any MRI contra-indications.

Participants prescribed medication for their ADHD were required to stop the medication five half-lives before the scanning session. Forty-seven participants had been prescribed medication for their ADHD, including 19 prescribed amphetamine, 24 methylphenidate, 4 non-stimulant medications. Participants also underwent a urine drug screen immediately before the scanning session and had to test free of drugs of abuse. Participants were compensated $150 USD for their time in completing measures and the imaging. The Institutional Review Board of the

university approved this study. The minor participants assented, and their parents provided informed consent. Participants 18 or older provided informed consent.

Factor Analysis. The purpose of the factor analysis was to reduce the data to a minimum number of factors that represent the latent construct of impulsivity. Our *a priori* hypothesis was that one factor would represent the shared variance among our impulsivity measures, although we allowed for the possibility that the tasks may load on different subcomponents of impulsivity. We implemented maximum likelihood factor analysis because it accounts for the covariance among variables, which is more appropriate for estimating latent factors than principal components analysis, which assumes orthogonal components (11). Missing data were imputed using mean imputation. The number of participants missing data from each task were as follows: BIS-II - 10, CAARS-Observer or CPRS - 12, Kirby delay discounting - 1, ZTPI - 53. This left a final N of 155 participants used in the factor analysis.

Graphical examination of the scree plot using the scree test revealed one meaningful factor [(12), Supplemental Figure S1]. This factor had an eigenvalue of 2.84 and explained 47.4% of the variance. We also found that our factor loadings agreed with our *a priori* assumption of loading direction. It is important to note that the second factor had an eigenvalue slightly greater than one (1.16) and explained 19.34% of the variance. If one were to use the Kaiser criterion, two factors are meaningful. However, the loadings on this factor are difficult to interpret (see Table 2 in the main text). Given the scree test, factor loadings, and difficulty in determining the psychological meaning behind the second factor, we chose to keep the first factor as our summary measure of impulsivity.

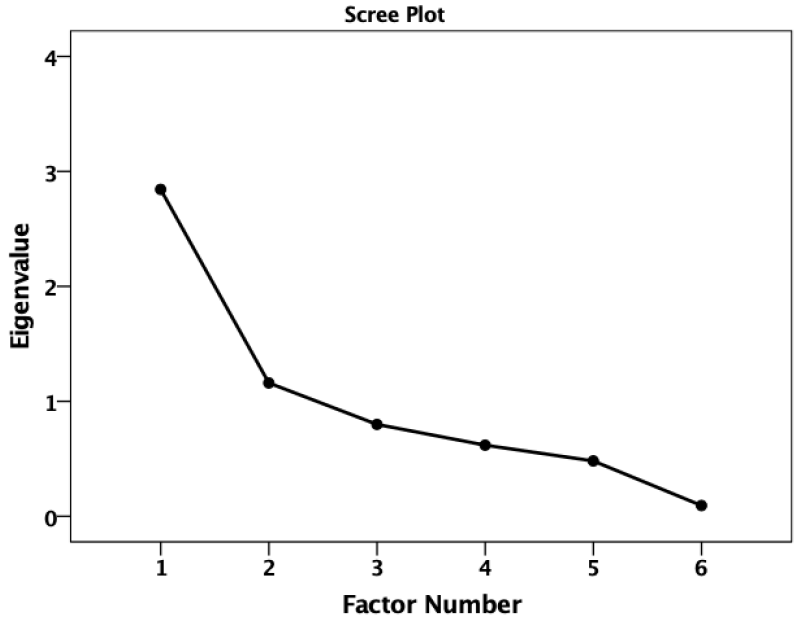

Figure S1. Scree plot from maximum likelihood extraction of impulsivity measures.

MRI acquisition, preprocessing, and analysis

Structural MRI. All neuroimaging data were collected at the University of California Davis Imaging Research Center. Before the scanning session, participants were screened and excluded for current drug use or pregnancy. Participants then completed a practice session that included a mock scan training session and the use of a dental rest. MRI scans were acquired on a Siemens 3T Trio scanner with a Tim upgrade (Siemens Healthcare, Erlangen, Germany). For each participant, high-resolution, T1-weighted structural images were collected using a co-planar, single shot, interleaved, 3D magnetization-prepared rapid gradient-echo (MPRAGE) in the sagittal plane (TR = 1900 ms, TE = 3.06 ms, FOV 256 mm, slice thickness 1 mm, slices per slab=192).

Diffusion-weighted MRI. Diffusion-weighted images were collected using 30 directions, with a total gradient diffusion sensitivity of b = 800 s/mm^2. We also acquired one B0 image, resulting in a 4D volume (dimension=128×128×70×31, voxel size=1×1×2 mm^3).

The diffusion-weighted data were processed using FSL (www.fmrib.ox.ac.uk/fsl). After correcting for movement and eddy current artifacts, the diffusion parameters were calculated for each voxel using FSL bedpostX. The measures of tract strength were calculated using probabilistic tractography (13, 14). Fiber tracking was conducted in parallel for each voxel within a predefined SN/VTA seed mask. We used 5,000 samples per voxel, a curvature threshold of 0.2, and a step length of 0.5 mm. Target areas in the striatum were defined using a connectivity-based segmentation atlas with subdivisions for sensorimotor, executive, and limbic regions; this atlas is freely available with the FSL software (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases/striatumconn). The striatal masks in MNI space were normalized to each participant's native space using the inverse of the spatial normalization parameters. To tailor the ROIs to each individual's anatomy, we used individually segmented gray matter (GM) and fractional anisotropy (FA) images to mask the ROIs. Following Tziortzi et al. (15), the lower threshold for the GM mask was set at 0.25, and the FA mask upper threshold was set at 0.40. The seed ROI for the SN/VTA was defined using a probabilistic atlas of human SN/VTA (16). We used a 50% probability threshold, and the mask was then normalized to each participant's native space using the inverse of the normalization parameters. To help tailor the ROIs to each individual's anatomy, we used each individual's brainstem image derived with freesurfer (17). This allowed the removal of any voxels that fell outside the brainstem.

All tractography analyses were conducted in the participants' native anatomical space. The FSL FDT toolbox was used to perform probabilistic tractography with a partial volume model (14), allowing for up to two fiber directions in each voxel (13). We generated 5,000 sample tracts from each voxel in the SN/VTA seed mask. Visual inspection was used to ensure that the tractography maps were successful and acceptable for further analysis. 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. Following standard procedures, the seed-based classification maps were first thresholded so that only voxels with at least 10 tracts terminating in one of the target regions were kept (18, 19). Next, the voxel values were converted into proportions of the number of tracts reaching the target mask from one voxel, divided by the number of tracts generated from that voxel (maximum 5,000). This resulted in 6 value maps per participant, one for each target region and each hemisphere (3 striatal regions × 2 hemispheres). We used the mean of these value maps as the measure of SN/VTA-striatum tract strength. Only participants with all 6 value maps were included in further analyses. This led to 5 participants being excluded (leaving the final N of 155).

Supplemental References

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