Supporting Online Material for

Dopaminergic Network Differences in Human Impulsivity

Joshua W. Buckholtz,* Michael T. Treadway, Ronald L. Cowan, Neil D. Woodward, Rui Li, M. Sib Ansari, Ronald M. Baldwin, Ashley N. Schwartzman, Evan S. Shelby, Clarence E. Smith, Robert M. Kessler, David H. Zald

*To whom correspondence should be addressed. E-mail: joshua.buckholtz@vanderbilt.edu

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Supporting Online Material

Materials and Methods

Participants

32 participants (mean age = 22.59 years, 16 male) were studied as part of an ongoing investigation of individual differences in striatal and extrastriatal DA release. All participants were medically and psychiatrically healthy adults, age 18 to 35, with estimated IQ greater than 80. Subjects were excluded if they had any history of substance abuse, current tobacco use, alcohol intake greater than 8 ounces of whiskey or equivalent per week, use of psychostimulants (excluding caffeine) more than twice in the subject's lifetime or at all in past 6 months, any psychotropic medication for the past 6 months other than occasional use of benzodiazepines for sleep, history of psychiatric illness, significant medical condition, any condition which would interfere with MRI or PET studies (e.g., extreme obesity, claustrophobia, cochlear implant, metal fragments in eyes, cardiac pacemaker, neural stimulator, and metallic body inclusions or other metal implanted in the body which may interfere with MRI scanning, pregnancy, or anemia). Female participants were studied during the early follicular phase of their menstrual cycle.

Following initial screening, subjects were given an interview of their medical history and a structured psychiatric interview (SCID-NP;(*S1*)). In addition to the regular questions in the non-alcohol substance dependence section of the SCID-NP, subjects were asked to indicate the number of times that they have taken any drug that they reported having tried, and asked to indicate any usage within the last 2 months. Any illicit drug use in the last 2 months was grounds for exclusion, even in subjects who did not

otherwise meet criteria for substance abuse. Urine drug screens were performed to test for the presence of amphetamines, cocaine, marijuana, PCP, and opiates, benzodiazepines, and barbiturates.

Personality and Behavioral Measures

Impulsivity was assessed with the 30-item Barratt Impulsiveness Scale, version 11 (BIS-11)(*S2*), which is one of the most widely used self-report measures of impulsive personality traits(*S3-S12*). In our sample of 32 subjects, BIS-11 scores ranged from 43 to 86, with a mean (standard deviation) of 59.47 (10.95). To measure subjective responses to amphetamine, we administered the Drug Effects Questionnaire (DEQ) at 60-minute intervals following the administration of drug and placebo. The DEQ consists of four questions: whether the subject feels the drug, whether the subject likes the drug, whether the subject feels high, and whether the subject wants more of the drug. Subjects indicated their response on a labeled magnitude scale (*S13*) from 0-100, with 0 indicating "Not At All" and 100 indicating "Most Imaginable." We used peak responses on the amphetamine day for our correlations with amphetamine-induced DA release.

PET

Image Acquisition and Analysis: All PET images were acquired using [^{18}F]fallypride. ((*S*)-*N*-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3[^{18}F]fluoropropyl)-2,3-dimethoxybenzamide), a substituted benzamide with very high affinity for D2/D3 receptors(*S14*). Unlike other D2/D3 ligands, [^{18}F]fallypride allows stable estimates of D2-like binding in both striatal and extrastriatal regions(*S*15). Our current resolution (see below) allows visualization of [18F]fallypride binding potential in the substantia nigra (SN)/ventral tegmental area

(VTA), [for a discussion of the spatial resolution requirements for detecting activity in the SN see (*S*16)]. However, this resolution does not permit us to cleanly distinguish between different DA cell populations, preventing a clear parcellation of the VTA from the neighboring SN, which possesses higher levels of D2-like receptors. Previous studies have demonstrated good intersubject and intratest-retest reliability for measurement of [^{18}F]fallypride binding potential for the DA midbrain at the current resolution(*S17-S19*). [^{18}F]fallypride binds with high affinity to both presynaptic ("D2-short") and postsynaptic ("D2-long") D2-like receptors(*S*20). However, because DA receptor expression in the midbrain is dominated by the D2-short receptor isoform (*S21*) variance in [^{18}F]fallypride BP_{ND} within the midbrain is presumed to be driven by individual differences in these D2-short autoreceptors.

In addition, [^{18}F]fallypride has been found to be sensitive to endogenous DA release (*S18,S22*), particularly in the striatum, making it an ideal ligand for use in conjunction with a dual scan strategy that allows assessment of both baseline receptor availability and individual differences in induced DA release. Baseline binding of [^{18}F]fallypride is also influenced by endogenous DA levels, and thus provides a metric of receptor availability, rather than absolute receptor density. However, receptor availability has proven a highly useful measure in quantifying individual differences in DA functioning, and indeed in some ways may be a more relevant variable than receptor density examined in isolation (as only available receptors can be engaged at a given point in time).

Protocols for PET image acquisition and analysis were derived from a larger ongoing study and have been previously published (*S18, S19*). Subjects received two PET scans using [^{18}F]fallypride. The first scan was a baseline placebo scan; the second scan was

performed while the subject received an amphetamine (d-AMPH) challenge. PET imaging was performed on a GE Discovery LS scanner located at Vanderbilt University Medical Center that was upgraded to a Discovery STE system during the course of the study. All subjects received their baseline and d-AMPH scans on the same scanner. To ensure the validity of combining data across scanners, we performed a voxel-wise analysis comparing DA release between the two scanners. No clusters survived whole brain correction at t = 2.5 (lowest cluster-level p-value >.90). Moreover, no differences were observed in striatal or midbrain anatomical regions-of-interest (ROIs). 12 participants were scanned on scanner 1, and 20 participants were scanned on scanner 2. BIS-11 scores did not differ significantly between participants scanned on scanner 1 versus scanner 2 ($p = 0.09$). Critically, partial correlation analysis confirms that scanner (scanner 1 vs. scanner 2) did not significantly affect any of the observed correlations between BIS-11 scores, midbrain D2/D3 availability and striatal DA (all p-values < 0.0005). Following reconstruction both scanners had similar in plane and throughplane resolution. [^{18}F]fallypride was produced in the radiochemistry laboratory attached to the PET unit, following synthesis and quality control procedures described in US Food and Drug Administration IND 47,245. Scans were timed to start 3 hours after 0.43mg/kg oral d-AMPH administration, which was timed to coincide with the period of peak plasma d-AMPH. 3-D emission acquisitions scans were performed following a 5.0 mCi slow bolus injection of [^{18}F]fallypride (specific activity greater than 3000 Ci/mmol). Serial scans were started simultaneously with the bolus injection of [^{18}F] fallypride and were obtained for approximately 3.5 hours, with two 15-minute breaks for subject comfort. CT transmission scans were collected for attenuation correction prior to each of the three emission scans.

Binding Potential Maps: Each subject's serial PET scans were first corrected for motion across scanning periods and then co-registered to the subject's structural T1-weighted MRI image (see *S*19 for details). To determine the success of the coregistration in the midbrain, in a prior study of 34 subjects(*S19*) we manually labeled several landmarks around the midbrain, including the posterior edge of the right and left inferior colliculus, the anterior-most point of the right and left cerebral peduncle and the interpeduncular fossa at $z = 10$, and the inferiormost point of the supramammillary commissure. Of these 34 subjects, all but one showed excellent midbrain coregistration, with no tag varying by 2mm in any direction from the mean coordinate of the tag (across these 33 subjects, the mean distance in any direction from the average tag was 1mm for every tag examined). Given the spatial resolution of the PET images, this degree of misregistration is at the subvoxel level, and would have negligible impact on the results.

Regional D2/D3 binding potential (nondisplaceable; BP_{ND}) was calculated on a voxelwise basis using the full reference region method(*S23*), with cerebellum chosen as the reference region because of its relative lack of D2/D3 receptors(*S24*). Voxelwise kinetic modeling was executed using Interactive Data Language. Prior studies in our lab indicate that the reference region method produces binding potential estimates that are in close agreement with estimates derived from Logan plots (*S25*) using a metabolite corrected plasma input function. Because [^{18}F]fallypride binding values exhibit significant variability across different regions (e.g., striatum vs. prefrontal cortex; PFC), we used variance estimates at the voxelwise level rather than the pooled variance used in typical parametric analyses (*S26*). Individual images of percent-change in [^{18}F]fallypride binding from placebo to amphetamine (representing percent-change in DA release) were created by

subtracting each subject's amphetamine scan from their placebo scan and dividing the resulting imaging by the placebo scan, using the "imcalc" image math routine in SPM5.

Group Correlation Maps: Prior to group analyses, a composite PET binding potential/T1-weighted MR image was created for each subject and warped to MNI space. The transformation matrix from this warping was then applied to the binding potential maps in order to bring all subjects data into a common space (MNI space). Group analyses of the PET data were performed in SPM5 by separately regressing subjects' BIS-11 scores against their D2/D3 binding (placebo) and amphetamine-induced DA release (percent-change) images. In all cases, gender was included as a covariate. SPMs were thresholded at $T > 3$; cluster threshold was set to 25 contiguous voxels. Only voxels within clusters surviving a cluster extent correction for multiple comparisons ($p_{corrected} < 0.05$) at this height threshold are reported.

Additional Statistical Analyses

[18F]fallypride binding: descriptive statistics

Baseline binding potential, midbrain [mean (SD)]: 2.72 (.42). Baseline binding potential, right striatum: 33.73 (3.66); Post-AMPH binding potential, right striatum: 25.98 (3.46). Baseline binding potential, left striatum: 30.75 (3.57); Post-AMPH binding potential, left striatum: 28.73 (3.15). Repeated-measures analysis of variance (ANOVA) confirms a significant decrease in striatal binding potential following AMPH administration: $F(1,31) = 306.99$, $p = 0.0000000000000001$(right striatum); $F(1,31) = 31.21$, $p = 0.000004$ (left striatum).

Partial Correlation Analyses

To control for the potentially confounding effects of variation in subject age, IQ

(measured using the Weschler Abbreviated Scale of Intelligence, Full Scale score, and available for 30 of our participants), amphetamine bioavailability, and the time window between placebo and amphetamine scans (range: 1-62 days, mean: 19 days), we used a series of two-tailed partial correlation analyses correlations within SPSS 17.0. BIS-11 scores were still significantly correlated with midbrain D2/D3 availability and both left and right striatal AMPH-induced DA release (all p-values for all analyses < 0.0005) even after controlling these potential sources of variability.

Correlations

To assess correlations between D2/D3 binding and AMPH-induced DA release, we calculated, for each subject, the first eigenvariate of the parameter estimate from the clusters identified in the group analysis (midbrain, right striatum and left striatum). We used two-tailed Pearson correlations within SPSS 17.0, with alpha = 0.05. These extracted eigenvariates were also used in similarly configured correlations with DEQ "Wanting" scores.

Mediation Analysis

We used the SPSS 17.0 macro *Indirect.sbs* (*S27*) to estimate the path coefficients and the size of the indirect effect of the multiple mediator model X (D2/D3 Binding) on Y (BIS-11 total scores) through Z (AMPH-induced DA release in left and in right striatum). DA release values for right and left striatum were modeled simultaneously. A Sobel test as implemented in *Indirect.sbs* was used to determine the significance of the difference in coefficient size between paths c (total effect) and c' (direct effect).

Supplementary Text

Given that we have previously reported a significant association between Novelty

Seeking and midbrain D2/D3 availability, we performed stepwise multiple regression analyses to determine if Novelty Seeking and BIS-11 scores uniquely and independently predict midbrain D2/D3 binding. This analysis demonstrated that BIS-11 score was an independent (and stronger) predictor of midbrain D2/D3 binding (BIS-11: $\beta = -0.728$, $p = 0.000002$; Novelty Seeking total: $\beta = -0.31$, $p = 0.08$; NS2: $\beta = -0.18$, $p = 0.2$). We note that this is a biased analysis in that the ROI was defined by the area of correlation with the BIS-11, rather than the area of correlation specified in our past paper on Novelty Seeking. Nevertheless, at least within a sizable portion of the midbrain, [^{18}F]fallypride binding potential appears more closely related to BIS-11 measured impulsivity than Novelty Seeking. We note also that it is possible that Novelty Seeking and BIS-11 are related to somewhat different portions of the DA midbrain, as neither correlation occupies the whole midbrain, but we are hesitant to make an explicit claim of regional specificity given the limitation in spatial resolution inherent to PET imaging. We also note that while an analysis of a "neutral" anatomical ROI could be performed, the practical application of such an ROI to the current analysis is complicated by the fact that it would, by necessity, include the entire midbrain, including elements that do not significantly express DA cell bodies. Moreover, the correlations for both personality scales do not even involve the entire DA midbrain, appearing to be more focused in the anterior and/or ventral portions. Unfortunately, there are no commonly applied anatomical templates that parse out separate portions of the DAergic midbrain, and MRI-defined anatomical boundaries for these regions in humans are poorly characterized, due in part to their poor contrast on standard T1-weighted anatomical scans.

To assess the extent to which BIS-11 scores were correlated midbrain D2/D3

binding and striatal DA release after controlling for variability in trait Novelty Seeking, we performed a partial correlation analysis controlling for individual differences in Novelty Seeking scores. Critically, the relationships between BIS-11 scores and both midbrain binding and striatal DA release were still highly significant, even after controlling for both Novelty Seeking total scores and NS2 subscale scores (midbrain D2/D3 binding: $p = 0.007$; right striatal DA release: $p = 0.01$; left striatal DA release: $p = 0.02$).

Taken together, these analyses indicate that while there is some degree of shared variance between the Novelty Seeking and BIS-11 scales in accounting for variability in the latent construct of impulsivity (which may account for the similarity in midbrain D2/D3 binding correlations for NS [Zald 2008] and BIS-11 scores [present manuscript]) there is a specific relationship between BIS-11 scores and midbrain D2/D3 receptor availability and striatal DA release that cannot be accounted for by variability in Novelty Seeking.

As some prior work suggests that trait impulsivity is associated with lower D2/D3 striatal receptor availability in the rodent(*S28*) and in human subjects with methamphetamine dependence(*S29*), it is important to rule out the possibility that individual differences in striatal D2/D3 receptor availability account for the observed positive correlation between trait impulsivity and striatal amphetamine-induced DA release. We did not find a significant relationship between BIS-11 scores and striatal D2/D3 availability, using either a whole-brain approach to correction for multiple comparisons, or an approach based on small-volume corrections within caudate, putamen, and nucleus accumbens regions of interest derived from the automated

anatomical labeling atlas (for caudate and putamen) and the Harvard-Oxford atlas (for nucleus accumbens). However, to confirm the absence of baseline receptor availability effects on our amphetamine-induced DA release/trait impulsivity finding, we specifically tested whether baseline striatal D2/D3 binding potentials could explain the association between striatal DA release and impulsivity. First, we extracted baseline binding values for each subject from left and right striatal regions of interest derived from our trait-impulsivity DA release correlation SPM. We confirmed via Pearson correlation analysis that there is no relationship between BIS-11 scores and D2/D3 baseline values ($p = 0.29$, right; $p = 0.26$, left) in this region. Next, we entered the extracted baseline binding values as a covariate of no interest in a multiple regression with striatal DA-release as the dependent variable and BIS-11 score a predictor of interest (i.e. an ANCOVA model). This analysis confirmed that the relationship between BIS-11 scores and amphetamine-induced DA release in the striatum is still significant ($p = 0.0003$, right; $p = 0.0001$, left) even after accounting for striatal D2/D3 baseline binding values.

We additionally performed a series of complementary ROI analyses to assess the relationship between BIS-11 scores and binding potential and DA release within the anatomically defined striatal subdivisions. Six ROIs (left/right dorsal caudate, left/right dorsal putamen, and left/right ventral striatum) were constructed by manually editing the striatum ROI derived from the LONI Probabilistic Brain Atlas 40 (LPBA40) according to the criteria outlined in Mawlawi et al. (2001). First, we correlated baseline D2/D3 binding in each of these regions with BIS-11 total scores. BIS-11 scores were not significantly associated with D2/D3 binding within any of these ROIs (all p-values > 0.1, with the exception of right dorsal caudate, where there was a trend-level correlation ($r =$

0.3, p = 0.08). Next, we correlated delta-BP (percent change between placebo and amphetamine scans) values in each of these regions with BIS-11 total scores. Consistent with the localization of our voxelwise correlations, we found significant associations between BIS-11 scores and AMPH-induced DA release in left ventral striatum (p = 0.004), right ventral striatum (p = 0.01), and right dorsal putamen (p = 0.04). Finally, we used partial correlation analyses to examine the significance of the correlations between BIS-11 scores and DA release values when controlling for baseline D2/D3 binding in each region. The correlation between AMPH-induced DA release and BIS-11 scores remained significant in right and left ventral striatum (p = .02, p = 0.007, respectively) after controlling for baseline D2/D3 binding, but the correlation for right dorsal putamen dropped to trend-level significance (p = 0.06).

These data make clear that the observed relation between AMPH-induced DA release in the ventral striatum is not simply a reflection of altered D2/D3 receptor availability. Taken as a whole, similarly strong conclusions cannot be made for more dorsal striatal divisions, but we must note that those topographically defined divisions only partially overlap the areas identified in voxelwise analyses, and given their size may have been insensitive to more discrete areas of association.

In considering the discrepancy between the present findings in humans compared to the results of Dalley and colleagues in rodents, it is instructive to consider two factors. First, there are important differences in the methods for assessing impulsivity between these two studies. Dalley et al utilized the 5-choice serial reaction time task (5-CSRT), a well-validated rodent paradigm that was designed as an analog of human continuous performance tests, which index performance during trials requiring the deployment of

sustained and divided attention (*S30*). Specifically, the frequency of premature responding in this task (nosepokes during an inter-trial interval preceding the presentation of a visual stimulus) is used as the basis for stratifying subjects on the basis of trait impulsivity. Importantly, there is robust evidence supporting both the significance of nucleus accumbens dopamine in mediating the rate of premature responding (*S31, S32*) and the relevance of trait differences on this measure for substance abuse (*S28, S33, S34*). Although this type of premature responding is clearly capturing an important and relevant aspect of impulsivity, at present its precise relationship to human facets of impulsivity is unclear, as there are no validated measures of this sort of premature responding in adult humans. This in no way weakens the importance of the Dalley et al. findings, but leaves open to question precisely what aspects of human impulsivity are homologous to premature responding in rodents. It is possible that the BIS-11 is not capturing the same facet of impulsivity as premature responding, that it is too broad of a measure to capture this specific dimension of impulsivity, or even that behavioral measures rather than self-report measures are necessary to capture this aspect of impulsivity. Future research using more fine-grained behavioral measures of impulsive responding and choice in humans will be necessary to parse the relationships between striatal D2/D3 binding and release and distinct subcomponents of the impulsiveness construct.

Additionally, inherent differences in dopamine anatomy and function between rodents and primates may also have played a role in the discrepant findings reported by Dalley et al compared to those communicated in the current paper. For example, the anatomical and functional organization of striatal projections both to and from the midbrain diverge markedly between rats and nonhuman primates(*S35*), as does the

regional distribution of dopamine receptor subtypes within the striatum(*S36, S37*). Further, rats express lower levels of dopamine transporter in the striatum, and perhaps consequently, require higher doses of psychostimulant drugs to manifest behavioral effects, compared to humans(*S38*). There is also some evidence from microdialysis for lower baseline DA levels in rats versus humans(*S39*). Moreover, much is still unknown about potentially other relevant species differences that might impact [^{18}F]fallypride measured D2/D3 binding. Future PET/microPET comparisons between rodents, non-human primates and humans will therefore be immensely useful in understanding how to interpret discrepancies between cross-species DA PET studies.

Finally, we note that Dalley et al. did not measure stimulant-induced DA striatal release, as we do here, but instead assessed baseline levels of DA metabolites using microdialysis. While this is important for ruling out potentially confounding effects of variation in endogenous DA levels that might account for differences in [^{18}F]fallypride BP in high impulsive rats, it does not exclude the possibility that, in analog to the current findings, high impulsive rats may show enhanced psychostimulant-induced striatal DA release.

The model presented in this paper proposes that decreased midbrain DA autoreceptor control exerts an influence on impulsivity at least partially through an enhancement of striatal DA release. In support of this model, we found a positive correlation between a trait measure of impulsivity and amphetamine-induced DA release in the striatum. The present results provide evidence that individual differences in midbrain DA functioning have a clear impact on impulsivity. That this effect is partially mediated by an influence on striatal DA release accords well with preclinical data

showing increased impulsivity in rodents (as measured by the 5-choice serial reaction task) following systemic and intra-accumbens amphetamine administration(*S32*), an effect which is blocked by 6-hydroxy-DA lesions of the nucleus accumbens (*S31*). The present result is also consistent with prior work showing that elevated striatal DA release following DA agonist administration is associated with risk for impulse control problems in Parkinsons Disease patients(*S40*).

In considering this model, it is important to reconcile our observed results with the known actions of amphetamine (AMPH) on mesolimbic DA circuitry. First, it is well established that, in general, D2/D3 autoreceptors provide a powerful mechanism for regulating midbrain DA neuron firing and impulse-dependent striatal DA release(*S41-S46*). However, AMPH is known to cause DA release in striatal terminals through a calcium-independent mechanism, primarily thought to result from reverse transport of DA from the presynaptic membrane to the synaptic cleft via a channel-like action of the DA transporter (though indeed, more recent studies suggest that even this mechanism is regulated by calcium signaling, and thus potentially influenced by impulse flow from midbrain neurons)(S*47-S50*). Further, AMPH can suppress midbrain DA neuron firing via dendritic release and striato-nigral feedback mechanisms (*S51-S55*). Critically, a wealth of evidence indicates that this suppressive effect of AMPH on midbrain DA neuron firing is autoreceptor-dependent. This is important for two reasons. First, individual differences in autoreceptor levels may influence the extent of this reduction in neuron firing following AMPH administration. Secondly, in the absence of adequate autoreceptor control (e.g. following intra-VTA D2 receptor blockade), AMPH actually exerts a powerful excitatory effect on midbrain neuron burst firing (*S54, S56*). Thus, our

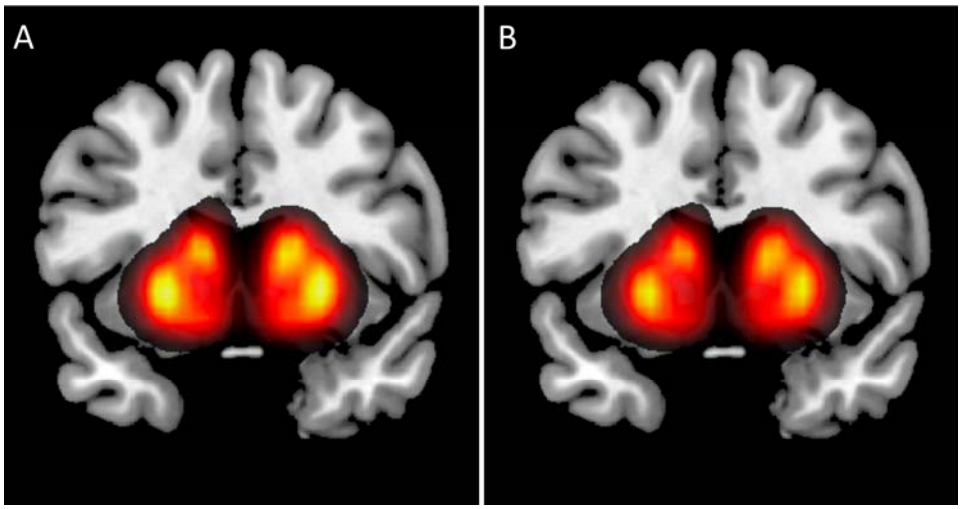
model would suggest that in impulsive individuals with low midbrain D2 receptor levels, AMPH may not only produce a smaller reduction in DA neuron firing, but may in fact lead to increased DA neuron burst firing. Enhanced midbrain neuron burst firing could lead to calcium-dependent exocytic release of DA from striatal terminals, which would, in turn, lead to higher synaptic DA levels than would be seen from the non-exoctyic actions of AMPH alone.

Importantly, it has been shown that the efficacy of the autoreceptor-dependent inhibitory feedback mechanism discussed above diminishes with repeated exposure to psychostimulants, and a reduction in autoreceptor function is thought to play a key role in stimulant sensitization (including sensitized striatal DA release) and the development of compulsive stimulant use (*S57-S59*). Thus, it is possible that, by altering the dynamics of feedback inhibition of midbrain DA neurons, diminished autoreceptor control in impulsive individuals could lead to enhanced stimulant sensitization, which may in turn contribute to the enhanced susceptibility to drug dependence in impulsive individuals (*S34*).

Finally, we note that in neurobiological association studies examining trait impulsivity, it is important to attend to the specific measure used to index impulsivity. We utilized the Barratt Impulsivity Scale, which taps motor, attentional, and cognitive aspects of impulsivity. Our finding stands in contrast to a recent PET study (*S60*), which described a negative correlation between the NEO-impulsivity facet and AMPH-induced displacement of striatal [^{11}C] raclopride. The NEO-impulsivity facet is an 8 item subscale that is a component of the NEO-Neuroticism scale, and primarily reflects an inability to resist urges(*S61*). Critically, the NEO-impulsivity scale is more closely related to anxiety

and other forms of negative emotionality, and indexes a different construct than the lack of deliberation and planfullness that are tapped by the Barratt Impulsivity Scale (see (*S62*))for factor analysis of measures of impulsiveness)**.** The Barratt Impulsivity Scale provides a more comprehensive assessment of impulsive traits, and has been more widely used in the impulsivity literature, because of its psychometric properties and more traditional conceptualization of impulsive traits.

Supplementary Figures



Supplementary Fig.1 Striatal [18F]fallypride binding potential for a representative subject, pre (A) and post (B) administration of 0.43 mg/kg d-AMPH. Images have been thresholded (min 5, max 50) to emphasize striatal BP, which is significantly higher compared to extrastriatal BP.

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