ARTICLE

Dopaminergic frontostriatal pathways in major depressive disorder and childhood sexual abuse: a multimodal neuroimaging investigation

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Dysregulated dopaminergic signaling has been implicated in the pathophysiology of major depressive disorder (MDD) and childhood sexual abuse (CSA), but inconsistencies abound. In a multimodal PET-functional MRI study, harnessing the highly selective tracer [^{11}C]altropane, we investigated dopamine transporter availability (DAT) and resting-state functional connectivity (rsFC) within reward-related regions among 112 unmedicated individuals (MDD: $n = 37$, MDD/CSA: $n = 18$; CSA no MDD: $n = 14$; controls: $n = 43$). Striatal DAT and seed-based rsFC were assessed in the dorsal and ventral striatum and the ventral tegmental area. We found that MDD, CSA, and their co-occurrence were associated with region-specific DAT abnormalities, which were related to the number of lifetime MDD episodes and the duration of childhood maltreatment. CSA was further associated with lower frontostriatal rsFC. The findings provide compelling evidence of DA dysregulation in MDD and CSA, and highlight potential prevention and treatment targets.

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INTRODUCTION

Early life stress (ELS) affects a range of domains including cognition [1] and reward circuity functioning [2, 3], and has been linked to various forms of psychopathology [4]. Indeed, ELS is a significant predictor of both child- and adult-onset psychiatric disorders [5, 6]; in particular, exposure to ELS increases individuals' risk for developing MDD prior to adolescence more than two-fold [7] and in adulthood [8], especially for females with a history of childhood sexual abuse (CSA; [9]).

Both ELS [10, 11] and MDD [12–14] have been linked to blunted reward-related activation within mesolimbic dopaminergic pathways as well as lower reward processing – particularly in reinforcement learning or response bias tasks, which rely on dopaminergic signaling [10, 15, 16]. Further, MDD and ELS have been linked to altered resting-state functional connectivity (rsFC) patterns of the bilateral putamen [17], activation in the caudate [18, 19], activation in the nucleus accumbens (NAcc; [2, 20]), and activation and rsFC of the ventral tegmental area (VTA; [14]). Indeed, work by Cheng and colleagues [21] showed that greater prefrontal-striatal rsFC was associated with more severe anxiety and depressive symptoms.

Coupled with behavioral findings, these task-based and resting-state fMRI patterns have been interpreted as reflecting blunted dopaminergic (DA) signaling, particularly in the midbrain and striatum. However, direct evidence of lower DA signaling remains scant. One possible marker of lower DA signaling is down-regulated dopamine transporter (DAT) availability, which has been observed in various preclinical models [22]. Lower DAT availability has been interpreted as suggesting a secondary downregulation of the transporter owing to low levels of DA [13].

In line with this assumption, using the highly selective DAT tracer [^{11}C]altropane, Pizzagalli and colleagues [23] reported that MDD was characterized by lower DAT availability in the putamen and DAT availability was lower with increasing number of lifetime depressive episodes. Of note, in the same study, lower putamen DAT was confirmed in postmortem tissue of patients with MDD [23].

In spite of compelling preclinical evidence linking various rodent models relevant to depression to lower DAT along mesolimbic pathway [24] and our initial findings of lower striatal DAT availability [23], evidence for DAT reduction in MDD has been inconsistent (e.g., [25]). We have argued that a possible reason for such inconsistencies might stem from the use of SPECT tracers that are not particularly selective for DAT [23].

It is unclear whether similar abnormalities in DAT availability are seen in the context of CSA. Researchers highlight the neurobiological overlap of stress and reward processing, postulating that the reward network is a primary contributor to the association between ELS and subsequent psychopathology; blunted dopamine transmission is likely related to altered reward processing [10, 13, 26].

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Our prior study, which included 23 controls and 25 individuals with MDD, was the first to use the highly selective DAT PET tracer [^{11}C]altropane in MDD [23]. To our knowledge, no study has examined DAT availability and functional connectivity in participants with vs. without MDD and/or CSA in the same study. Accordingly, the goals of the current study were to: (1) replicate the earlier report of lower striatal DAT binding potential in MDD in a larger sample ($n = 46$ included in a previous study), hypothesizing that participants with MDD would demonstrate blunted DAT in the putamen [23]; (2) examine CSA-related differences in DAT, hypothesizing that CSA would be related to blunted DAT in all striatal regions of interest; and (3) probe rsFC within reward-related circuitry and possible relations to striatal DAT.

METHODS

Participants and study design

Adults (ages 18–45) across four groups: controls, MDD, CSA/no MDD, and MDD/CSA were recruited from the Boston metropolitan area between 2012–2016 for two separate studies. The objective of Study 1 ($n = 46$; 67% female) was to evaluate possible dopamine dysfunction in MDD and the objective of Study 2 ($n = 66$; 100% female) was to probe dopamine mechanisms after CSA and identify possible biomarkers of resilience to MDD. Therefore, only Study 2 examined CSA and ELS variables.

Across both studies, all participants were unmedicated and right-handed, had no contraindications for undergoing magnetic resonance imaging, had no neurological or medical illnesses, and had no lifetime substance dependence or substance abuse in the last year. Participants with MDD were not considered for the study if they were taking any psychotropic medications in the past 2 weeks (6 weeks for fluoxetine), had lifetime use of dopaminergic drugs, and had psychiatric comorbidities (with the exception of social anxiety disorder, generalized anxiety disorder, or specific phobia if MDD was the primary concern). More information regarding inclusion and exclusion criteria are summarized in the Supplement. 114 unmedicated participants completed: (i) a clinical assessment visit, (ii) an MRI session (approximately 2 weeks after the clinical visit), and (iii) a PET imaging visit (approximately 1 month after the clinical visit). One participant was excluded from PET analyses due to benzodiazepine use during the PET imaging visit and one participant was excluded from all analyses for unreliable reporting. In addition, one participant lacked fMRI data, and three participants were excluded from fMRI analyses due to in-scanner motion (Supplementary Methods). Thus, the final sample included 112 individuals with PET data and 109 individuals with rsfMRI data. We discovered that one control participant had a history of MDD; therefore, we conducted a sensitivity analysis excluding this participant.

The clinical assessment included a DSM-IV structured clinical interview [27] to confirm current diagnosis of, or absence of lifetime, MDD. In addition, participants completed a variety of clinical assessments: the Traumatic Antecedents Questionnaire [28], the Hamilton Rating Scale for Depression (HRSD; [29]), the Beck Depression Inventory (BDI-II; [30]), the Snaith Hamilton Pleasure Scale (SHAPS; [31]), their history of major depressive episodes (MDE; binned (see Supplementary Results) and continuously), and the Mood and Anxiety Symptom Questionnaire (MASQ; [32]), which are described in the Supplementary Methods. Study 2 included a pharmacological manipulation (a single 50 mg administration of the D2/3 antagonist amisulpride vs. placebo) during the fMRI visit, however, this manipulation was designed to affect later fMRI tasks and was previously shown not to influence rsFC measures [33] (Supplementary Methods). Drug administration (amisulpride, placebo, none) was controlled for within fMRI analyses (see below). In addition, we conducted sensitivity analyses excluding all participants receiving amisulpride.

Ethics approval and consent to participate

All study procedures were performed in accordance with the relevant guidelines and regulations and approved by the Partners Healthcare Institutional Review Board (reference numbers: 2009P001360 and 2012P002593). We obtained informed consent from all participants, and they were compensated for their participation.

PET

As reported in Pizzagalli and colleagues [23], participants were placed in the PET scanner with head alignment adjusted relative to the canthomeatal line. A thermoplastic mask was used to reduce motion and a peripheral venous catheter was inserted for radiopharmaceutical injection of intravenous [^{11}C] altropane injection (~10 mCi delivered over 20–30 seconds). More information regarding the dose can be found in Supplementary Table S1. Scans were acquired over 60 min 39 frames of increasing duration using an ECAT EXACT HR + (CTI, Knoxville, TN) PET scanner. Images were reconstructed with corrections for scatter and attenuation, random coincidences, system deadtime, and detector inhomogeneity. Frames were motion-corrected and aligned to subject-specific MPRAGE in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). More information regarding FSL preprocessing can be found in the full article [23].

Our regions of interest included the left and right putamen, caudate, NAcc, and VTA. Regional binding potential (BP_{ND}) was estimated using the multilinear reference tissue model with the cerebellum (excluding the vermis) as reference region [34, 35]. Left and right striatal BP_{ND} was defined using the Harvard-Oxford Subcortical Probabilistic Atlas (50% threshold; [36, 37]. The VTA mask was manually traced based on established guidelines [38, 39] – mirroring and bisecting lateralized volumes of interest (visually checked to overlay the VTA on the MNI atlas). Each mask consisted of 81 voxels (with 2 mm isotropic dimensions).

MRI data acquisition and preprocessing

MRI datasets were collected at the McLean Imaging Center on a 3 T Siemens Tim Trio using a 32-channel head coil (Supplementary Methods). Resting-state fMRI data were preprocessed using fMRIPrep [40] and additional denoising steps were conducted in CONN toolbox ([41]; Supplementary Methods).

Functional connectivity within the reward circuit

Region of interest (ROI)-ROI functional connectivity analysis was conducted within the following nodes of the reward circuit [42]: right and left caudate, right and left putamen, right and left NAcc, anterior cingulate cortex (ACC), and the ventromedial prefrontal cortex (vmPFC). Subcortical regions and the ACC were parcellated using the Harvard-Oxford atlas [43]. The vmPFC ROI was defined as a 10 mm sphere centered on [6.98, 53.58, −4.78], using coordinates derived from a previous meta-analysis of reward processing [44] (see Supplementary Fig. S1 for a glass-brain image indicating ROIs used in the analysis). Functional connectivity between pairs of nodes was calculated by computing Pearson's correlations between the average BOLD time series from all pairs of nodes, followed by Fisher's transform.

Striatal DAT-functional connectivity associations

To examine relationships between DAT and rsFC, seed-based FC was computed in CONN for the following seeds (ROIs): the bilateral caudate, putamen, and NAcc. FC between the seed and every voxel in the brain was computed by Pearson's correlations between the seed's BOLD time series and each individual voxel BOLD time series. Last, Fisher's transform was applied to correlation values.

Statistical analyses

Clinical, demographic, and PET data were analyzed in *R*. Between-group differences in clinical and demographic variables were tested using ANOVAs and chi-squared tests. For PET data, we conducted one MANCOVA, to examine main effects of MDD, CSA, and MDD/CSA interaction on DAT availability in our bilateral regions of interest: the putamen, caudate, NAcc, and VTA, controlling for age at the PET scan (as age has been linked to reduction in DAT BP_{nd}; [45, 46]) and a factor variable for "Study". Drug status (amisulpride, placebo, none) was controlled for in rsFC analyses. If groups differed on demographic characteristics or variables that could affect dopamine (e.g., smoking status, caffeine use), we conducted a sensitivity analysis to test if our findings were robust to additional covariates.

Statistical analyses of rsFC and DAT-FC association were conducted in CONN toolbox, controlling for age, study, and drug administration (amisulpride, placebo, none). For functional connectivity within the reward circuit, the main effects of MDD, CSA, and MDD x CSA interaction were tested using a general linear model (GLM). A Functional Network Connectivity (FNC; [47]) cluster-based inference was used, with a threshold of FDR-corrected cluster-level $p < 0.05$ (multivariate parametric omnibus test). Associations between DAT and seed-based FC across participants were tested using a GLM with FC as the dependent variable and DAT as the independent variable. A statistical threshold of voxel-level $p < 0.001$, FDR-corrected cluster-level $p < 0.05$ was applied.

When there was a main effect of group on DAT availability or rsFC, we examined the relation between these ROIs and clinical variables. We focused on the most relevant variables: number of lifetime depressive episodes in the presence of a main effect of MDD; duration of ELS in the presence of a main effect of CSA; and lifetime depressive episodes and duration of ELS in the presence of a MDD x CSA interaction.

RESULTS

Sample characteristics

Characteristics of groups are summarized in Table 1 and the Supplement. The CSA/no MDD and MDD/CSA group had a higher proportion of females compared to the controls and MDD participants, as was expected based on the study sources from which the sample was drawn (see Participants, above). Further, caffeine consumption in the last 24 h was highest in the MDD/CSA group ($n = 1$ consumed 1360 mgs of caffeine on the day of the PET scan; information regarding caffeine consumption estimation can be found in the Supplementary Methods). Age, race, education, average caffeine consumption, and the proportion of current smokers did not differ between groups.

Those with CSA, on average, were 7.81 years old ($SD = 3.14$) at the start of the abuse, experienced a 3.72 severity of abuse ($SD = 1.11$; with a 5 indicating the most severe), with an average duration of 4.06 years of abuse ($SD = 3.27$). Within the CSA group, there were no differences in age of sexual abuse onset ($t(30) = 1.84$, $p = 0.075$), sexual abuse severity ($t(30) = -1.67$, $p = 0.106$), or sexual abuse duration ($t(30) = -1.79$, $p = 0.084$) in those with MDD compared to those without MDD.

MDD and CSA effects on striatal DAT

When modeling all 8 ROIs simultaneously using a MANCOVA, significant main effects were observed for CSA ($F_{8,99} = 2.07$, $p = 0.045$) and age ($F_{8,99} = 3.57$, $p = 0.001$); MDD ($F_{8,99} = 1.94$, $p = 0.063$), the covariate 'Study' ($F_{8,99} = 1.76$, $p = 0.093$), and the MDD X CSA interaction ($F_{8,99} = 1.40$, $p = 0.205$) were not statistically significant in the overall multivariate model.

Follow-up univariate ANOVAs were conducted to examine these effects within each brain region. Individuals with MDD had lower DAT in the left putamen ($F_{1,106} = 7.10$, $p = 0.009$) (Fig. 1A). In contrast, individuals with CSA had significantly higher DAT in the left caudate ($F_{1,106} = 4.06$, $p = 0.047$; Fig. 1B) and right VTA ($F_{1,106} = 8.58$, $p = 0.004$; Fig. 1C). There was a significant MDD x CSA interaction in the right NAcc ($F_{1,106} = 4.00$, $p = 0.048$) (Fig. 1D) where individuals in the MDD/CSA group had the lowest DAT. There were also significant main effects of age in the left putamen ($F_{1,106} = 7.21$, $p = 0.008$), left caudate ($F_{1,106} = 7.54$, $p = 0.007$), and right caudate ($F_{1,106} = 15.18$, $p < 0.001$) with significantly lower DAT with age. There was a main effect of Study in the left NAcc ($F_{1,106} = 4.75$, $p = 0.032$); participants in Study 1 had significantly higher DAT (Study 1 $M = 1.99$, $SD = 0.54$; Study 2: $M = 1.83$, $SD = 0.60$). We obtained a similar pattern of findings when conducting a sensitivity analysis excluding the participant with MDD in the control group and adding additional covariates (smoking status, biological sex, and caffeine consumption in the last 24 h) that differed across our four groups (Supplementary Results).

Lower frontostriatal rsFC for individuals with CSA

A main effect of CSA was found for two clusters of rsFC within the reward circuit, indicating lower frontostriatal rsFC for individuals with CSA (Table 2 and Fig. 2). Specifically, in CSA, lower rsFC was found between the medial prefrontal cortex, comprising the vmPFC and ACC, and the bilateral putamen [cluster 1: $F_{2,100} = 7.35$, p FDR cluster-corrected $= 0.010$]; as well as the bilateral caudate [cluster 2: $F_{2,100} = 5.77$, p FDR cluster-corrected $= 0.021$]. Similar results were obtained after excluding participants receiving amisulpride (Supplementary Fig. S2).

DAT-rsFC associations in the striatum

DAT in the left putamen was negatively associated with left putamen—left OFC rsFC (MNI: [−46 20 −8], cluster size: 261 voxels, $p = 3.7{\cdot}10^{-4}$ FDR cluster corrected) (Fig. 3A, B). Since a main effect of MDD on DAT was found in the left putamen, a post hoc analysis examined whether the DAT-rsFC relation was present and similar within MDD and non-MDD groups. DAT and rsFC were significantly associated in both groups (MDD: p DAT $= 0.008$; no MDD: p DAT $= 7.9{\cdot}10^{-5}$; Fig. 3C, D).

DAT in the right caudate was negatively associated with three rsFC patterns: (i) right caudate—left dorsolateral prefrontal cortex (dlPFC) (MNI: [−14 50 46], cluster size: 151 voxels, $p = 8.8{\cdot}10^{-3}$ FDR cluster corrected) (Fig. 4A, C); (ii) right caudate—right dlPFC (MNI: [14 52 42], cluster size: 127 voxels, $p = 0.021$ FDR cluster corrected) (Fig. 4A, D); (iii) right caudate–left OFC (MNI: [−52 26 −4], cluster size: 115 voxels, $p = 0.033$ FDR cluster corrected (Fig. 4B, E). Findings remained when excluding participants receiving amisulpride (Supplementary Fig. S3).

Relation between DAT, rsFC, and clinical symptoms

A higher number of lifetime major depressive episodes were related to lower age-residualized DAT availability in the left putamen ($rs(99) = -0.23$, $p = 0.018$). When depressive episodes were considered along a continuum, as opposed to bins, we obtained a similar result, however it decreased to a trend-level ($rs(42) = -0.25$, $p = 0.099$). The duration of ELS was not related to DAT in the left caudate or right VTA (all $ps > 0.285$) and lifetime depressive episodes did not contribute to DAT in the right NAcc ($p = 0.790$). However, a longer duration of ELS was related to lower DAT availability in the right NAcc ($F_{1,46} = 4.97$, $p = 0.031$). For seed-based rsFC within the CSA groups, ELS duration was also positively related to rsFC of the left putamen–left OFC rsFC ($F_{1,42} = 5.24$, $p = 0.027$) and right caudate—left OFC ($F_{1,42} = 6.37$, $p = 0.016$).

DISCUSSION

Dopamine, which is highly correlated with DAT availability [22], has been hypothesized to play a critical role in the development and maintenance of depression [13, 48]. Further, individuals who experience CSA are more likely to develop depression [8]. Less is known, however, regarding mechanisms underlying depressive symptoms and DAT availability. Indeed, although we have different sources of evidence linking DAT availability to depression, and CSA to depression, prior research has failed to unite these in a single investigation or link DAT dysfunction to other neurobiological mechanisms. Further, PET imaging studies tend to have small sample sizes. Here, we examined the independent and compounding role of MDD and CSA on DAT availability in key striatal regions in a relatively large sample of unmedicated individuals involving four groups: MDD (absent, present) x CSA (present, absent).

Among 112 well-characterized adults, we found that DAT availability differed as a function of MDD and a history of CSA. Specifically, confirming our earlier report [23] in a larger sample, MDD was related to lower DAT availability in the putamen. Further, more depressive episodes were negatively associated with DAT availability in this region; however, these findings were not robust (i.e., similar effect sizes, but statistical trend) when restricting the analyses to participants with MDD and therefore should be interpreted provisionally. Notably, CSA was related to higher DAT availability in the left caudate and right VTA, though there were no associations with ELS duration. There was a significant interaction between MDD and CSA in DAT availability of the right NAcc; specifically, those with a history of CSA and MDD had the lowest DAT availability. We found that a longer duration of ELS was related to lower DAT availability in the right NAcc. CSA, but not MDD, was linked to lower frontostriatal rsFC.

Table 1. Demographic and clinical characteristics of the sample.

	Controls $n = 43$ *n* (%) or *M* (*SD*)	CSA no MDD $n = 14$ *n* (%) or *M* (*SD*)	MDD $n = 37$ *n* (%) or *M* (*SD*)	MDD / CSA $n = 18$ *n* (%) or *M* (*SD*)	Statistic
Female	33 (76.7%)	14 (100%)	32 (86.5%)	18 (100%)	$\chi^2(3) = 8.55$, $p = 0.036$
Age	26.80 (6.97)	25.36 (5.57)	25.99 (5.71)	29.50 (6.60)	$F(3108) = 1.53$, $p = 0.212$
White ($n = 3$ missing data)	27 (62.79%)	6 (42.86%)	28 (75.68%)	9 (50.00%)	$\chi^2(3) = 6.60$, $p = 0.086$
Education ($n = 1$ missing data)	15.61 (2.84)	15.79 (1.72)	16.30 (2.45)	15.13 (2.00)	$F(3107) = 1.01$, $p = 0.390$
Average caffeine consumption ($n = 1$ missing data)	107.92 (79.73)	57.14 (54.73)	113.47 (90.77)	132.11 (93.57)	$F(3107) = 2.29$, $p = 0.083$
Caffeine 24 h before PET ($n = 2$ missing data)	91.93 (110.23)	52.93 (69.33)	91.57 (81.82)	224.78 (303.24)	$F(3106) = 4.63$, $p = 0.004$
Current smokers ($n = 2$ missing data)	3 (7%)	0 (0%)	3 (8.1%)	0 (0%)	$\chi^2(3) = 2.63$, $p = 0.453$
Income ($n = 2$ missing data)					
<$10,000	2	NA	3	3	$\chi^2(15) = 14.93$, $p = 0.457$
$10,000–$25,000	13	3	13	4	
$25,000–$50,000	11	5	9	7	
$50,000–$75,000	9	5	3	1	
$75,000–$100,000	4	NA	5	2	
>$100,000	4	1	2	1	
Lifetime MDE ($n = 11$ missing data)					
1 MDE	NA	NA	6 (16.2%)	3 (16.7%)	NA
2–3 MDEs	1 (2.3%)	NA	13 (35.1%)	6 (33.3%)	
≥5 MDEs	NA	NA	12 (32.4%)	4 (22.2%)	
HRSD ($n = 5$ missing data)	1.10 (2.30)	1.79 (2.61)	15.85 (4.71)	15.29 (3.20)	$F(3103) = 158.3$, $p < 0.001$
BDI-II ($n = 4$ missing data)	1.50 (4.00)	2.29 (3.05)	28.11 (8.98)	28.15 (10.17)	$F(3104) = 122.60$, $p < 0.001$
SHAPS ($n = 4$ missing data)	21.32 (7.14)	22.00 (5.91)	32.91 (5.80)	30.94 (5.89)	$F(3104) = 26.21$, $p < 0.001$
MASQ GDA ($n = 4$ missing data)	12.56 (1.80)	13.50 (2.71)	22.38 (7.27)	25.09 (7.27)	$F(3104) = 36.48$, $p < 0.001$

(*MDD*) Major depressive disorder, (*CSA*) childhood sexual abuse, (*PET*) positron emission tomography, (*MDE*) major depressive episodes, (*HRSD*) Hamilton Rating Scale for Depression, (*BDI*) Beck Depression Inventory II, (*SHAPS*) Snaith Hamilton Pleasure Scale, (*MASQ GDA*) Mood and Anxiety Symptom Questionnaire General Distress: Anxious Symptoms.

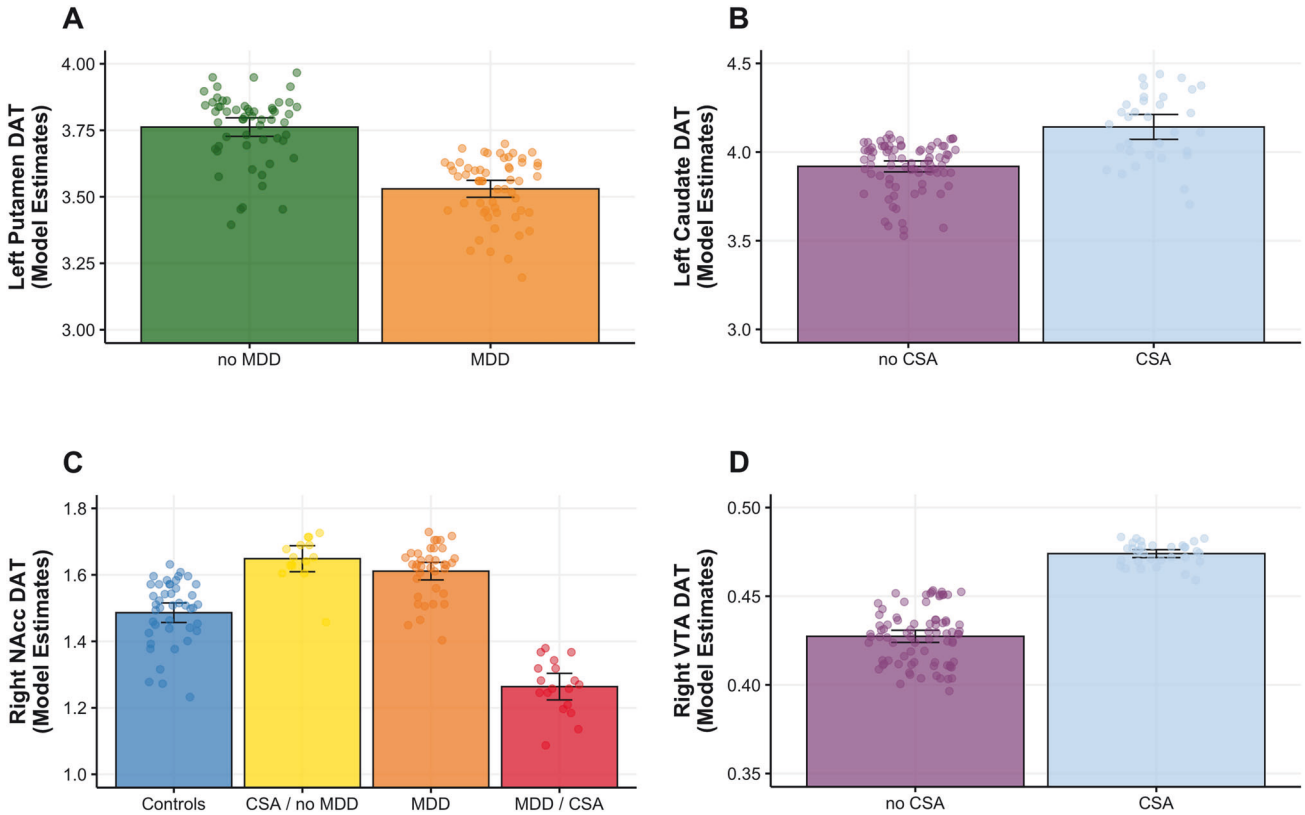

Fig. 1 Main effects and interactions of MDD and CSA on DAT BP_{nd}. DAT dopamine transporter, NAcc nucleaus accumbens, VTA ventral tegmental area, MDD major depressive disorder, CSA childhood sexual abuse. **A** left putamen, **B** left caudate, **C** right NAcc, **D** right VTA.

Table 2. Main effect of CSA on resting-state functional connectivity within the reward circuit.

ROI-ROI functional connection	Statistics	*P* uncorrected	*P* FDR corrected
Cluster 1	**$F_{2,100} = 7.35$**	**0.001050**	**0.010499**
L putamen – vmPFC	$t(101) = -3.14$	0.002242	0.013897
L putamen – ACC	$t(101) = -2.95$	0.003970	0.013897
R putamen – vmPFC	$t(101) = -3.06$	0.002871	0.020099
R putamen – ACC	$t(101) = -2.42$	0.017375	0.060811
Cluster 2	**$F_{2,100} = 5.77$**	**0.004264**	**0.021320**
L caudate – vmPFC	$t(101) = -3.42$	0.000897	0.006278
R caudate – vmPFC	$t(101) = -2.92$	0.004269	0.029881
L caudate – ACC	$t(101) = -2.61$	0.010363	0.036270
R caudate – ACC	$t(101) = -2.27$	0.025543	0.089402

ACC anterior cingulate cortex, *L* left, *R* right, *vmPFC* ventromedial prefrontal cortex.

Specifically, individuals with a history of CSA, whether currently experiencing MDD or no psychopathology, showed weaker rsFC between the medial prefrontal cortex and the bilateral striatum.

The current findings linking MDD to lower DAT availability are consistent with and extend previous work. For example, a meta-analysis examining 43 studies found that DAT availability was lower in individuals with MDD compared to controls [49]. More specifically, individuals with MDD were characterized by lower DAT in the putamen [23, 50] and VTA [23]. Finally, lower DAT in the putamen was also observed in postmortem tissue. Additional work examining geriatric patients found that those with MDD have lower DAT in the NAcc and putamen compared to controls [51].

Previous findings relating early life stress to dopamine functioning in humans are mixed [52]. While some studies have reported positive associations between childhood trauma and dopamine release (e.g., [53]), others have observed negative associations (e.g., [54]). This may be due to varying definitions and measurements of stress, clinical groups, and sample characteristics. One study found that participants exposed to severe physical or sexual abuse had higher dopamine synthesis capacity in the striatum [55]. We extended these findings by identifying higher DAT in the left caudate and right VTA related to CSA.

However, consistent with the literature, we found associations in the opposite direction as well. Specifically, the MDD x CSA interaction was related to the lowest DAT availability, and longer ELS duration was negatively associated with DAT in the right NAcc. Our findings suggest that experiences of MDD and CSA reflect distinct neural profiles, which is consistent with prior work [56]. The significant MDD x CSA interaction suggests that depression in the context of CSA is the most impactful on DAT

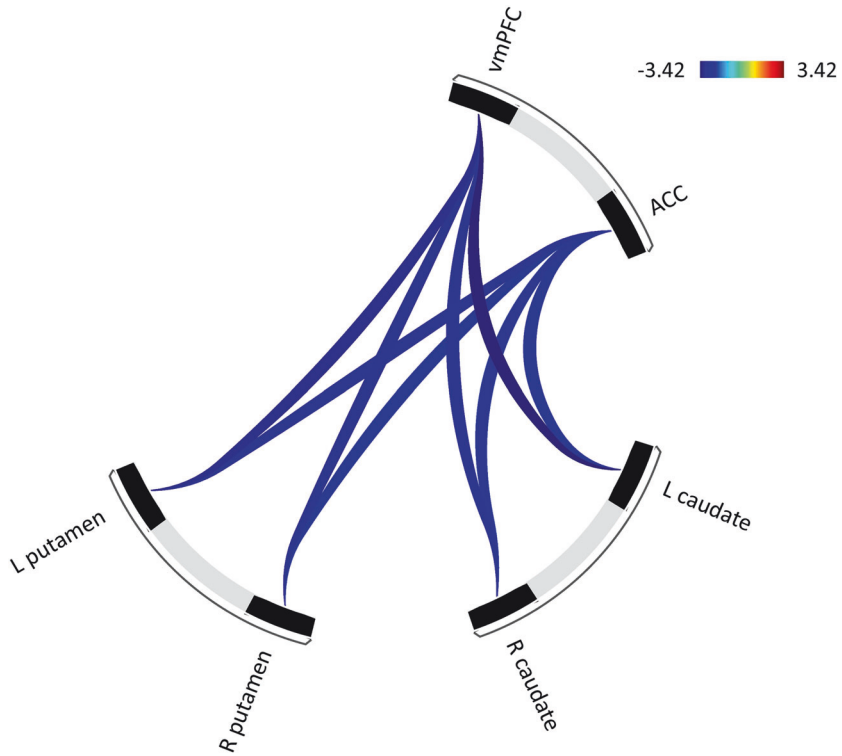

Fig. 2 Main effect of childhood sexual abuse (CSA) on resting-state functional connectivity within the reward circuit. Individuals with a history of CSA exhibited lower resting-state functional connectivity between (i) the medial prefrontal cortex (vmPFC and ACC) and the bilateral putamen [cluster 1: $F_{2,100} = 7.35$, p FDR cluster-corrected = 0.010]; and between (ii) the medial prefrontal cortex (vmPFC and ACC) and the bilateral caudate [cluster 2: $F_{2,100} = 5.77$, p FDR cluster-corrected = 0.021].

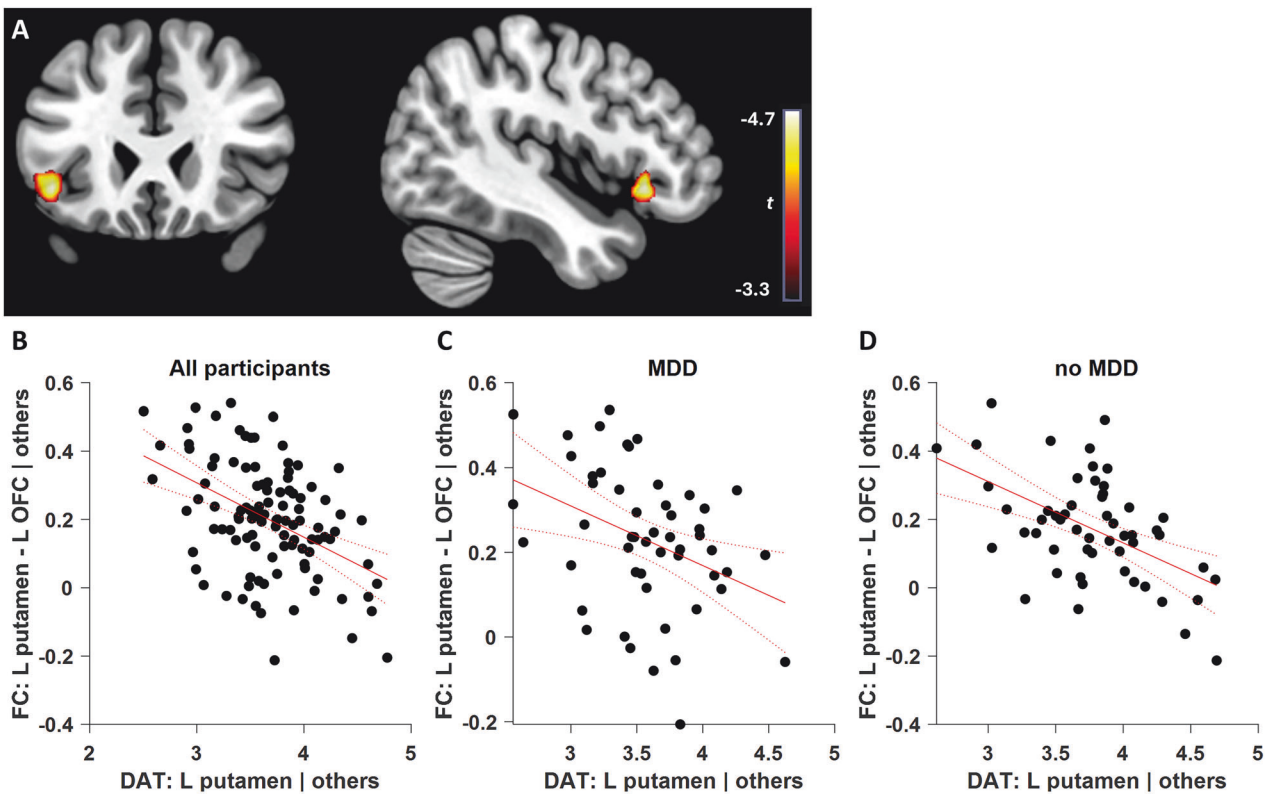

Fig. 3 Left putamen DAT – rsFC association. A DAT in the left putamen was negatively associated with rsFC between the left putamen and left OFC. The level of DAT- rsFC association is shown by the colorbar. **B** Partial regression plot indicating the relationship between left putamen DAT (x axis) and left putamen—left OFC rsFC (y axis), while controlling for age, study, and drug administration (amisulpride, placebo, none). A follow-up analysis showed that DAT-rsFC association was found in both **C** MDD (p DAT = 0.008) and **D** non-MDD (p DAT = $7.9{\cdot}10^{-5}$) groups.

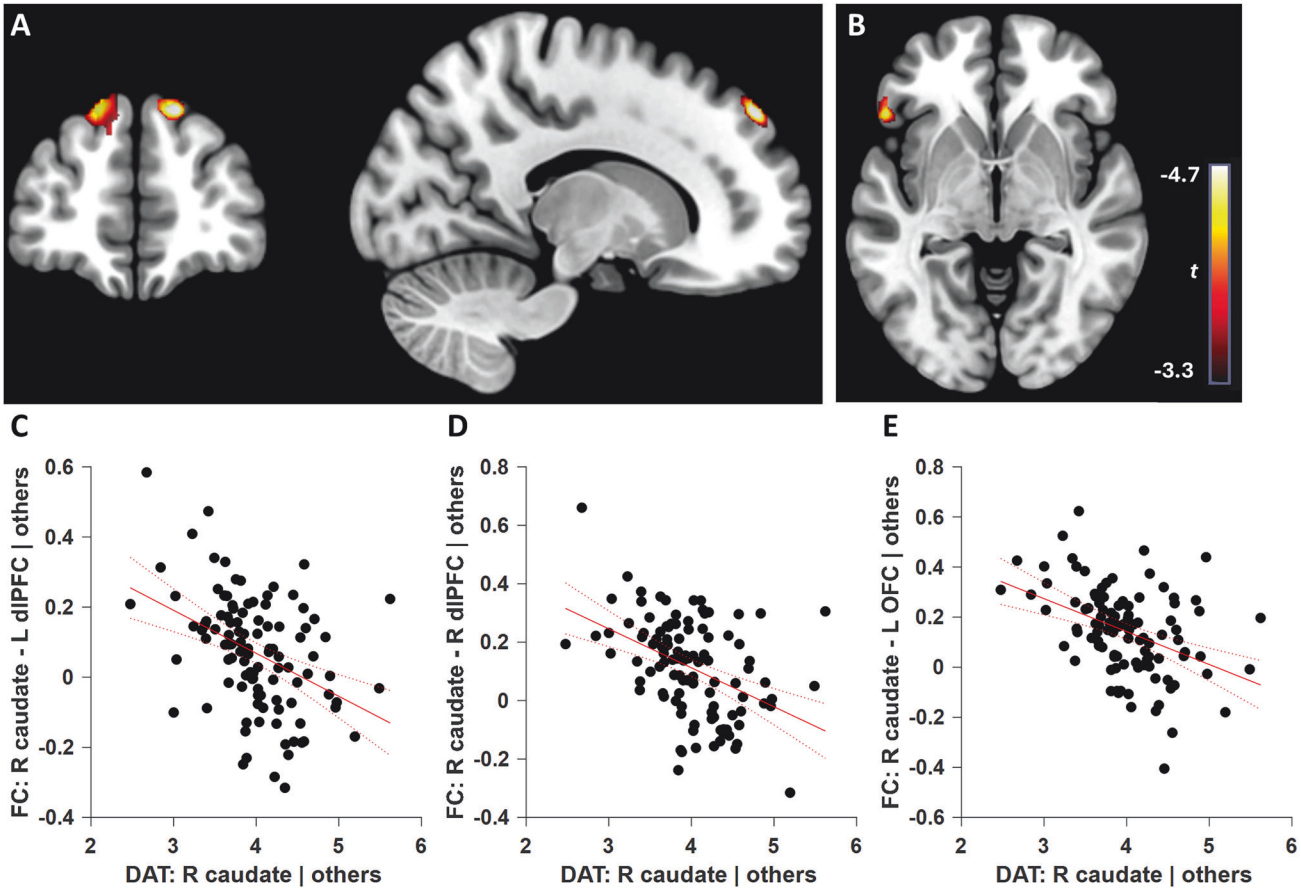

Fig. 4 Right putamen DAT – rsFC association. DAT in the right caudate was negatively associated with: **A** rsFC between right caudate and left and right dorsolateral prefrontal cortices (dlPFC); **B** rsFC between right caudate and left OFC. The colorbar shows the level of DAT- rsFC association. **C-E** Partial regression plots indicating the relationship between right caudate DAT (x axis) and right caudate rsFC (y axis), while controlling for age, study, and drug administration (amisulpride, placebo, none).

availability in the right NAcc, which may account for differences in reward sensitivity and symptoms. Participants with a history of CSA but no MDD did not have blunted DAT availability; which may reflect a compensatory or resilient response. This idea is broadly consistent with models of stress resilience proposed by Charney and colleagues [57], who hypothesized that adaptive dopamine function in mesolimbic regions may underlie individual differences in vulnerability to trauma. Supporting this, preclinical work by Krishnan and colleagues [58] using a social defeat paradigm has shown that gene expression patterns differ between "Susceptible" and "Unsusceptible" mice, and that experimentally reducing brain-derived neurotrophic factor release from the VTA to NAcc, or blocking such signaling, can promote resilience. Though speculative, the current findings may reflect a similar mechanism in humans. More research is needed to understand the relation between ELS, CSA, and dopamine functioning in humans.

CSA, across MDD and no MDD status, was associated with weaker rsFC between the bilateral striatum and medial prefrontal cortex. This finding aligns with a previous report of lower rsFC within the reward circuit for adults with moderate to severe childhood ELS, irrespective of MDD diagnosis [59]. Weaker reward circuit rsFC in individuals with childhood ELS adds to previous literature that mostly focused on limbic regions (e.g., amygdala, hippocampus) and has identified lower FC within frontal-limbic networks [60, 61], although findings have been mixed [62].

DAT in the left putamen and right caudate was negatively associated with rsFC with the left OFC and bilateral dlPFC. Namely, higher striatal DAT availability was associated with weaker striatal-lateral prefrontal rsFC. To our knowledge, this is the first study to investigate DAT-rsFC patterns across the brain in MDD or ELS. Notably, elevated DAT levels lead to higher dopamine clearance and lower dopamine signaling, consistent with our finding of an inverse association between DAT and rsFC. Of relevance, previous work has shown that striatal DAT was negatively associated with deactivation of the DMN during a visual attention task [63]. In addition, DAT values were found to map to a second-order functional connectivity gradient within the striatum [64].

Limitations

Though this study has a number of notable strengths including a large PET imaging sample size, a focus on only unmedicated participants, and multimodal neuroimaging, we should note four limitations. First, this work is not experimental, therefore, we cannot make inferences as to whether the observed differences preceded the development of MDD or were a consequence of MDD and or CSA. Second, although we controlled for this in the rsfMRI analyses and the main findings remained when excluding the 46 participants receiving a single low dose of amisulpride before the rsfMRI scan, this study design for ~42% of our sample (46/109) potentially limits the generalizability of our findings. Third, due to its focus on CSA, Study 2 only included women; therefore, we could not assess resilience or the interaction of MDD x CSA in male participants. Finally, some of our effect sizes were small (particularly the MDD x CSA interaction with the right NAcc) and additional work examining these effects will strengthen our understanding of the interplay between clinical groups, dopamine, and symptoms.

CONCLUSIONS

By utilizing a multimodal PET-fMRI investigation, our findings unveiled and clarified the differential and compounding impacts of MDD and CSA on the reward circuit. Ultimately, these results suggest distinct neurobiological markers of MDD and early life stress, and highlight promising targets for prevention and treatment.

DATA AVAILABILITY

De-identified datasets will be shared upon reasonable request to the corresponding author.

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AUTHOR CONTRIBUTIONS

LRB: Conceptualization; Formal analysis; Investigation; Methodology; Resources; Visualization; Writing - Original draft; Writing – Review & Editing. RD: Conceptualization; Formal analysis; Investigation; Methodology; Resources; Visualization; Writing - Original draft; Writing – Review & Editing. ELB: Investigation; Project administration; Resources; Writing – Review & Editing. RHK: Investigation; Project administration; Resources; Writing – Review & Editing. RC: Investigation; Project administration; Resources; Writing – Review & Editing. FG: Investigation; Project administration; Resources; Writing – Review & Editing. PP: Investigation; Project administration; Resources; Writing – Review & Editing. MB: Investigation; Project administration; Resources; Writing – Review & Editing. DW: Investigation; Project administration; Resources; Writing – Review & Editing. GEF: Investigation; Project administration; Resources; Writing – Review & Editing. MDN: Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Writing – Review & Editing. DAP: Conceptualization; Funding acquisition; Methodology; Resources; Supervision; Writing – Review & Editing.

COMPETING INTERESTS

Over the past 3 years, DAP has received consulting fees from Arrowhead Pharmaceuticals, Boehringer Ingelheim, Circular Genomics, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, Neurocrine Biosciences, Neuroscience Software, and Takeda; he has received honoraria from the American Psychological Association, Psychonomic Society and Springer (for editorial work) as well as Alkermes; he has received research funding from the BIRD Foundation, Brain and Behavior Research Foundation, Dana Foundation, Millennium Pharmaceuticals, National Institute Mental Health, and Wellcome Leap; he has received stock options from Ceretype Neuromedicine, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software. MB is employed by Lyra Health and Lyra Clinical Associates, receives income from Lyra Health and Lyra Clinical Associates, and has been granted equity in Lyra Health. All other authors report no financial relationships with commercial interests.

ADDITIONAL INFORMATION

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Dopaminergic Frontostriatal Pathways in Major Depressive Disorder and Childhood Sexual Abuse: A Multimodal Neuroimaging Investigation

Supplemental Information

Supplementary Methods

Supplementary Results

Supplementary Methods

Assessments of early life stress

Participants in Study 2 completed the Traumatic Antecedents Questionnaire (1) which indexes a variety of stressors. Participants indicated the severity of each stressor on a scale of 1 to 5 (1 indicating that the stressor experienced was “not at all” upsetting, 5 indicating that the stressor experienced was “extremely” upsetting). We calculated the duration of ELS based on the total number of years that participants’ experienced limited caretaking, was verbally bullied, physically bullied, had alcohol or substance abuse problems in the family, heard verbal aggression between parents, witnessed physical aggression between parents, was involved in an abusive relationship with a significant other, experienced verbal abuse, experienced spanking with an object, experienced physical abuse (slapping, hitting/beating, other), experienced sexual abuse, and experienced sexual aggression, from ages 0 to 18.

Assessments of depression and anxiety

The Hamilton Rating Scale for Depression (HRSD; (2)), Beck Depression Inventory (BDI-II; (3)), and Snaith Hamilton Pleasure Scale (SHAPS; (4)) are widely used measures of depression and anhedonia and have good psychometric properties. The HRSD was administered by a clinician to assess the severity of depression and consisted of 17 items; the BDI-II provides a self-reported measure of depression severity and consists of 21 items, and the SHAPS assesses anhedonia and consists of 14 items; we used the total score for all depressive measures. We also measured the number of lifetime major depressive episodes (MDE; n=11 with missing data). In line with Pizzagalli

and colleagues (5) and given the distribution of the data, we binned the sample into 0 MDEs (*n*=56), 1 MDEs (*n*=9), 2-4 MDEs (*n*=20), and ≥5 MDEs (*n*=16). [See also *Rationale for Binning Number of Major Depressive Episodes* in the Supplementary Results]. The Mood and Anxiety Symptom Questionnaire (MASQ; (6)) is a widely used instrument that measures symptoms of depression, anxiety and general distress and consists of 62 items; given our other assessments examining anxiety, we focused on the General Distress: Anxious Symptoms (GDA) subscale.

Inclusion/exclusion criteria

Participants in the control group were excluded if they had a history of psychiatric disorders, if they had a family history of mood disorders or psychosis, or ever took psychotropic medication. In Study 2, participants were also excluded if they reported their first maltreatment or abuse occurring between age 13 to 18 on the Traumatic Antecedents Questionnaire (1), had a lifetime history of mania, anorexia, bulimia or posttraumatic stress disorder in the last 2 years, or a head injury, or cognitive or language impairments that interfered with their ability to participate.

Pharmacological manipulation during MRI visit

Study 2 involved a pharmacological manipulation in a double-blind placebo-controlled design, where participants received a single dose of 50 mg amisulpride (hypothesized to increase dopaminergic signaling via autoreceptor blockade) or a placebo (see (7)). The drug was administered before the fMRI scan, such that the peak plasma concentration of amisulpride (i.e., 1 hour after administration) coincided with the

beginning of the monetary incentive delay task, which followed the resting-state scan. Notably, previously published work showed that this pharmacological manipulation did not impact resting-state functional connectivity measures (8). Please note that amisulpride was administered only once during the fMRI session; thus, the PET data were not affected.

MRI data acquisition

Resting-state fMRI data were acquired using a single-band gradient-echo echo-planar imaging (GE-EPI) sequence with the following parameters: TR=3 sec, TE=30 ms, image matrix=72×72, in-plane field of view=216x216 mm, flip angle=85°, voxel size=3x3x3 mm, 47 interleaved slices, with a total of 124 measurements. Anatomical images were acquired using a high-resolution T1-weighted multi-echo MPRAGE sequence with TR=2.2 sec, TE= 1.54, 3.36, 5.18, 7ms, in-plane field of view=230x230 mm, voxel size=1.2x1.2x1.2 mm, 144 slices. The T1-weighted images were acquired for coregistration and normalization of the functional MRI and PET images.

MRI data preprocessing

Preprocessing of MRI data (anatomical, resting-state) was done in fMRIPrep 20.2.1 (9). The following description of the preprocessing steps was taken from the custom language generated by fMRIPrep, which is recommended for use in publications and has been released under the CC0 license. *Anatomical data preprocessing:* The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.3.3 (Avants et al.

2008), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9, Zhang, Brady, and Smith 2001). Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, Dale, Fischl, and Sereno 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (Klein et al. 2017). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with antsRegistration (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: ICBM 152 Nonlinear Asymmetrical template version 2009c [Fonov et al. (2009), TemplateFlow ID: MNI152NLin2009cAsym], FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model [Evans et al. (2012), TemplateFlow ID: MNI152NLin6Asym].

Functional data preprocessing: First, a reference volume and its skull-stripped version were generated by aligning and averaging 1 single-band references (SBRefs). A deformation field to correct for susceptibility distortions was estimated based on fMRIPrep's fieldmap-less approach. The deformation field is that resulting from co-registering the BOLD reference to the same-subject T1w-reference with its intensity inverted (Wang et al. 2017; Huntenburg 2014). Registration is performed with antsRegistration (ANTs 2.3.3), and the process regularized by constraining deformation

to be nonzero only along the phase-encoding direction and modulated with an average fieldmap template (Treiber et al. 2016). Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration (Greve and Fischl 2009). Co-registration was configured with six degrees of freedom. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9, Jenkinson et al. 2002). BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207 (Cox and Hyde 1997). First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. The BOLD time-series were resampled onto the following surfaces (FreeSurfer reconstruction nomenclature): fsaverage. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. The BOLD time-series were resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space.

fMRI data denoising

Further denoising of the resting-state fMRI data was conducted in CONN toolbox (10). Confounds were regressed out utilizing the anatomical component-based noise correction (aCompCor; 11). These included: (i) Outlier scans, identified based on the amount of subject in-scanner motion as measured by the framewise displacement (FD)

and global BOLD signal. Acquisitions with FD > 0.9mm or global BOLD signal changes > 5 standard deviations were considered outliers and removed by regression. (ii) First 5 principal components (PCAs) of the CSF and white matter signals: regressed out to minimize the effects of physiological non-neuronal signals such as cardiac and respiratory signals. (iii) Estimated subject-motion parameters and their first-order derivatives (a total of 12 parameters). (iv) Session effects: A step function convolved with the hemodynamic response function was used to remove potential effects of the beginning of the session. In addition, the linear BOLD signal trend was regressed out. Note that global signal regression was not performed. After regression of all potential confounding effects, temporal band-pass filtering (0.008-0.09 Hz) was performed.

Three participants were excluded from fMRI analyses due to in-scanner motion, i.e., >20% outlier volumes.

Supplementary Results

Sample characteristics

As expected, MDD and MDD/CSA groups had higher scores on depression (HRSD; BDI), anhedonia (SHAPS), and anxiety (MASQ) measures relative to control participants and individuals with CSA who did not develop psychopathology (statistics reported in Table 1). The sample was racially and ethnically diverse, with 34.82% reporting as non-white. Annual income ranged from less than $10,000 to more than $100,000, and education ranged from 7-24 years. The average age of onset of CSA was 8.09 years old (*SD*=3.48; range 1-17) with a mean severity=3.70 (*SD*=1.10; range 1-5).

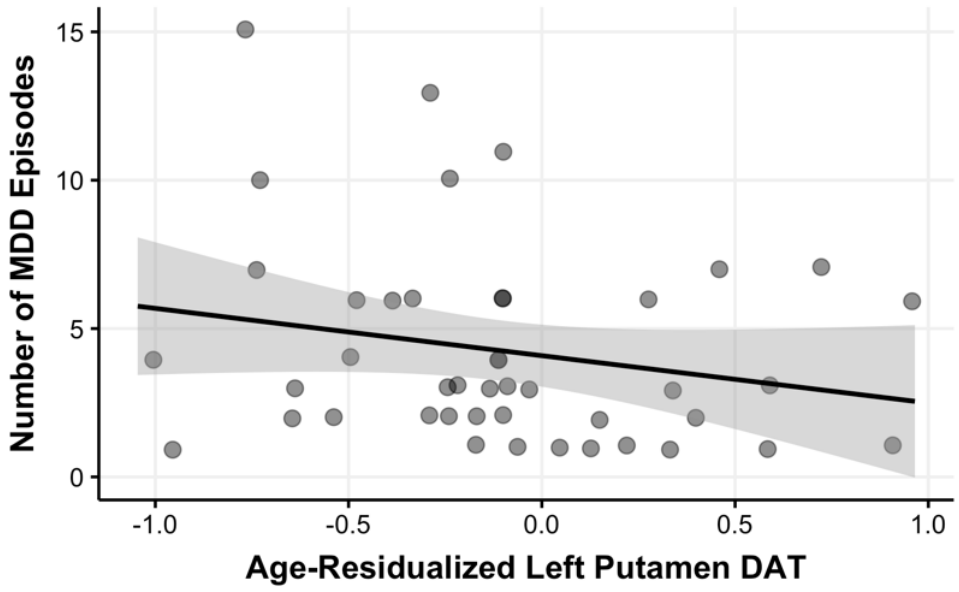
Rationale for binning number of major depressive episodes

As in prior studies from our laboratory, we binned number of lifetime major depressive episodes for conceptual and methodological reasons. Conceptually, our prior studies using this strategy demonstrated significant morphological/structural and molecular differences. For example, Treadway et al (12) identified morphometric changes in the dentate gyrus and medial prefrontal cortex associated with 1, 2-4 or more than 5 lifetime MDEs, and Pizzagalli and colleagues (5) found that the same binning (0, 1, 2-4 or >5) was inversely associated with dopamine transporter binding potential in the putamen and ventral tegmental area. In our prior studies, we had conceptualized that having zero, a single lifetime MDE or more than five likely captured clinically salient subgroups (i.e., individuals who never developed MDD, individuals who avoid recurrence after a single episode vs. those who have multiple recurrences through their life); the 2-4 lifetime MDEs subgroup was selected to be an intermediary group.

Moreover, Monroe & Harkness (13) provide compelling commentary regarding the nature of recurrent depression specifically supporting that “recurrence” is not met with a second episode, rather it should be thought of as a positively skewed distribution for individuals who are not prone to depression and a bimodal distribution for individuals who are recurrence prone (see Figure 1 from that paper). More work is needed to understand what factors distinguish individuals with depression who are and are not recurrence prone, supporting grouping in this way. There is also an inherent logic related to the frequency of recurrence of depression at the point of data collection to this grouping strategy. That is, a person with 0 or 1 MDEs has no recurrence at that time, while a person with 2-4 MDEs has some recurrence, and a person with 5+ MDEs has substantial recurrences. From a methodological perspective, many individuals in the “more than 5 MDEs” reported that they had had “too many episodes to know for sure”. In light of this, in the current and our prior work, we felt it was more conservative and parsimonious to use this 4-bin subgroups.

Continuous analysis of major depressive episodes

We provide the scatterplot for the continuous analysis of MDE below.



Note. One participant was 3 SDs above the mean and had ~2.5X more depressive episodes (35 MDEs) than the next highest participant (15 MDEs) and was therefore excluded from this analysis).

Caffeine consumption estimation

For each subject, the amount of caffeine consumed regularly and on the day before the session was be assessed. For caffeine, the Nutrition Data System (14) was be used to estimate the milligrams of caffeine in different drinks.

Sensitivity analyses for PET data

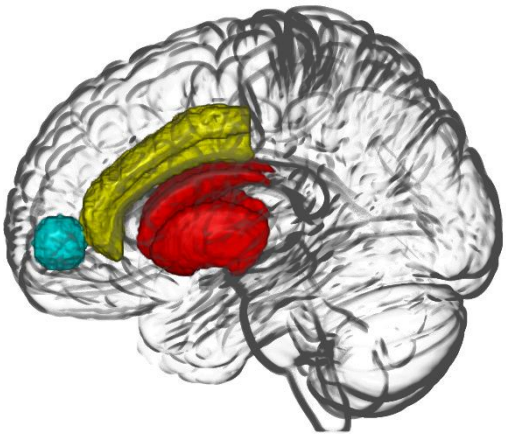
We conducted sensitivity analyses excluding one control participant with a history of MDD, and controlling for smoking status, biological sex, and caffeine consumption in the last 24 hours, in addition to our original covariates of study and age. We obtained a similar pattern of findings (left hemisphere: main effect of MDD: $F_{4,97}$=2.52, p=.046; main effect of CSA: $F_{4,97}$=2.83, p=.029; main effect of age: $F_{4,97}$=4.11, p=.004; right hemisphere: main effect of CSA: $F_{4,97}$=2.73, p=.034; main effect of age: $F_{4,97}$=5.29, p<.001; interaction of MDD x CSA: $F_{4,97}$=1.96, p=.106). Smoking status, biological sex, and caffeine consumption in the last 24 hours did not contribute unique variance to DAT values in the left (all ps>.628) or right hemisphere (all ps>.205).

Supplementary Table S1: PET doses

	Controls ***n*=43** ***M* (*SD*)**	**CSA no MDD** ***n*=14** ***M* (*SD*)**	**MDD** ***n*=37** ***M* (*SD*)**	**MDD / CSA** ***n*=18** ***M* (*SD*)**	**Statistics**
Injected Activity (MBq)	348.34 (22.18)	344.54 (69.71)	339.77 (21.60)	351.55 (25.59)	F(3,106)=0.73, *p*=.536
Specific Activity at TOI (GBq/μmol)	113.95 (93.01)	86.70 (20.57)	112.29 (91.43)	88.14 (17.70)	F(3,106)=0.76, *p*=.521
Injected Mass (nmol)	4.45 (3.27)	4.11 (0.86)	4.81 (5.58)	4.14 (0.89)	F(3,106)=0.17, *p*=.915

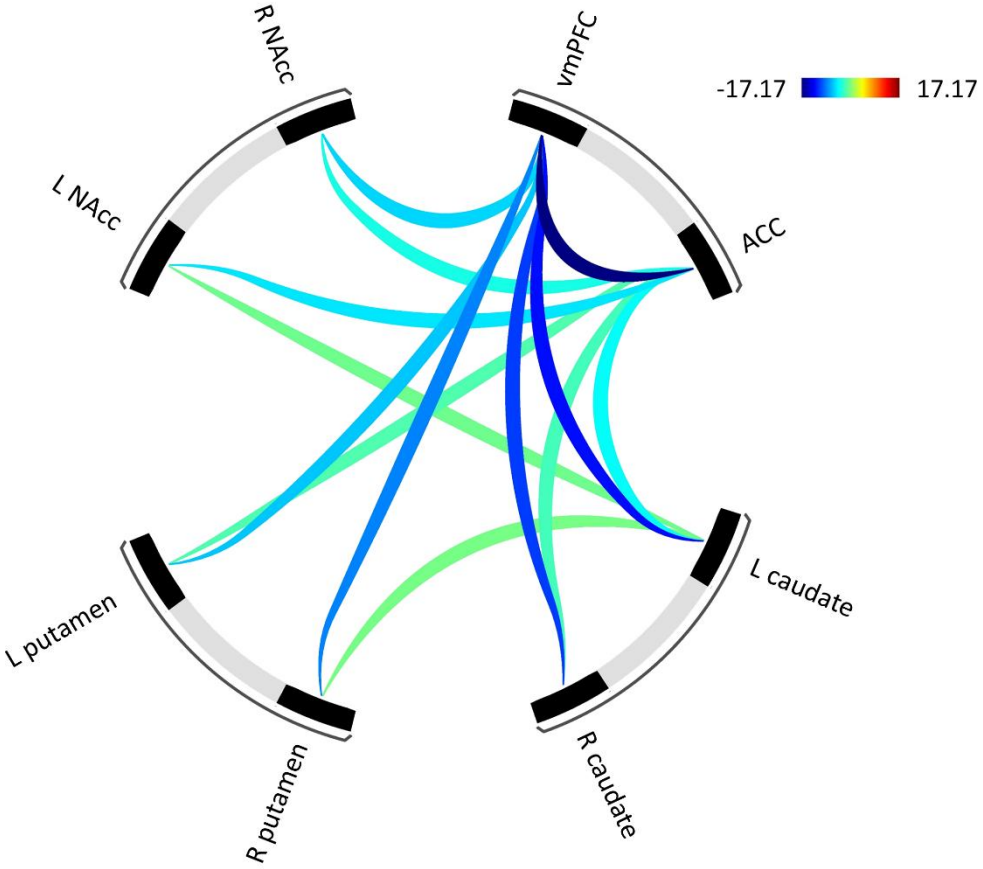
Note. Data missing for 2 participants (*n*=1 CSA no MDD; *n*=1 MDD/CSA).
MBq=megabecquerels; GBq=gigabecquerels per micromole; TOI=Time of Injection; nmol=nanomoles

Supplementary Figure S1. Glass-brain image indicating ROIs



The caudate, putamen, and nucleus accumbens are indicated in red; the anterior cingulate cortex (ACC) is presented in yellow; and the ventromedial prefrontal cortex (vmPFC) is indicated in light blue.

Supplementary Figure S2. Sensitivity analysis for resting-state functional connectivity (rsFC)

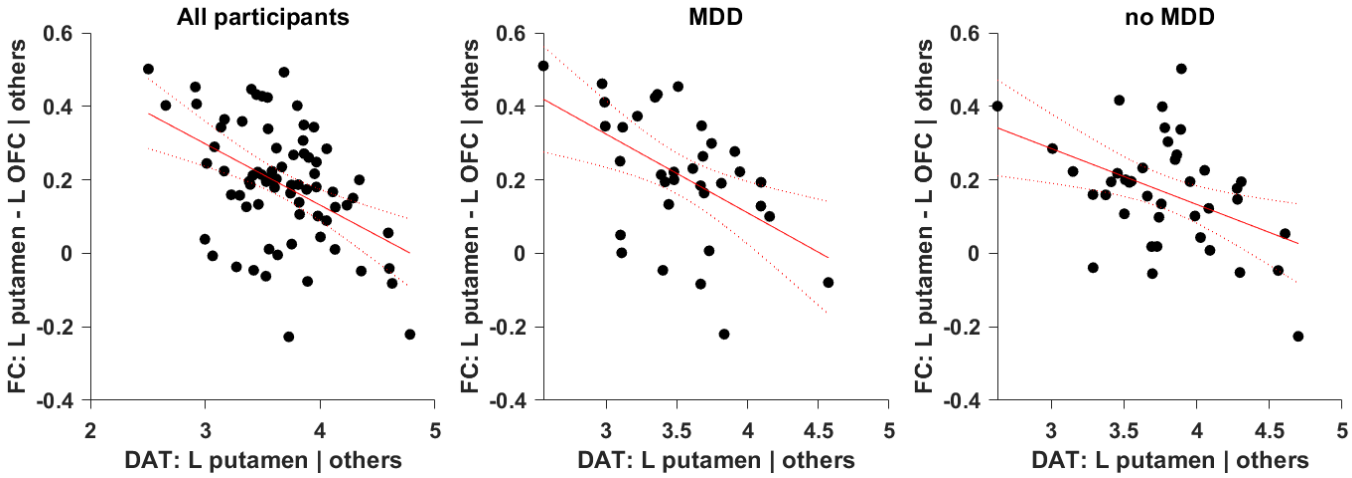


Sensitivity analysis was carried out on the sample after excluding individuals who received amisulpride prior to the MRI scan, resulting in a total sample of 74 individuals. Similar findings were obtained. Specifically, individuals with a history of CSA exhibited reduced resting-state functional connectivity between the medial prefrontal cortex, comprising the vmPFC and ACC, and the striatum (putamen, caudate, NAcc). In addition, the functional connectivity between the vmPFC and ACC was also reduced for individuals with CSA.

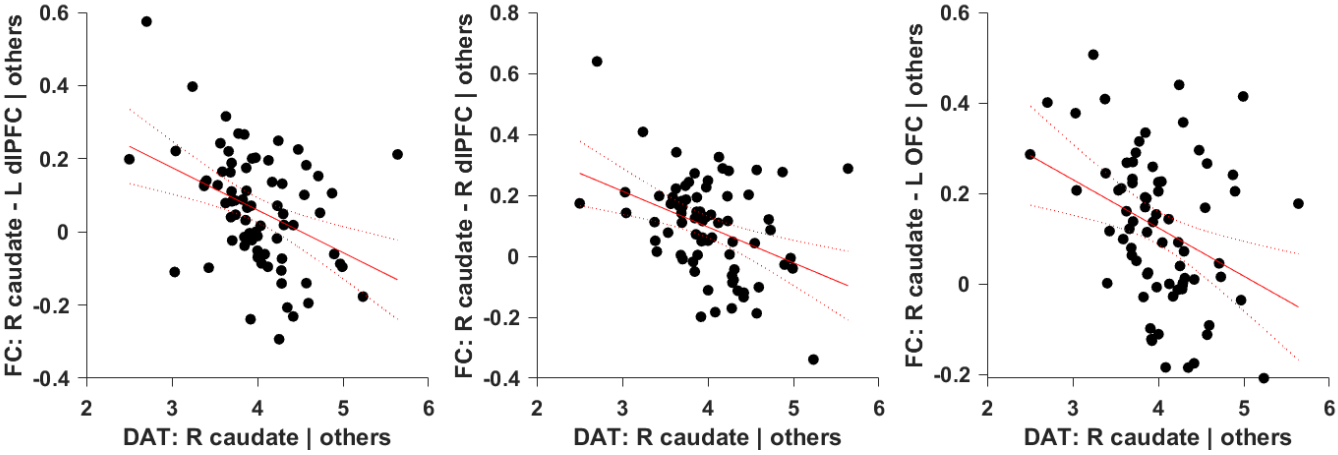
Note, that a non-parametric cluster-level inference was used due to the smaller sample size: Threshold Free Cluster Enhancement (TFCE; 15), which thresholds ROI-to-ROI parametric maps while appropriately controlling the family-wise error rate, using a *p* FWE-corrected <0.05 connection-level threshold. This is a standard setting for cluster-based inferences available within CONN toolbox.

Supplementary Figure S3. Sensitivity analysis for dopamine transporter availability (DAT)-rsFC associations

Left putamen:



Right caudate:



DAT-rsFC analyses were repeated after excluding individuals who received amisulpride prior to the MRI scan, resulting in a total sample of 74 individuals.

For all clusters previously identified, DAT remained a significant predictor of rsFC:

<u>Top row:</u>

Left putamen – left OFC:

(left) all individuals: p DAT = $4.9 \cdot 10^{-5}$

(middle) MDD only: p DAT = 0.003

(right) non-MDD only: p DAT = 0.006

Bottom row:

(left) Right caudate – left dlPFC: p DAT = $5.0 \cdot 10^{-4}$

(middle) Right caudate – right dlPFC: p DAT = $6.8 \cdot 10^{-4}$

(right) Right caudate – left OFC: p DAT = 0.002

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