European Neuropsychopharmacology 57 (2022) 39–49

www.elsevier.com/locate/euroneuro

The effects of acute dopamine depletion on resting-state functional connectivity in healthy humans

Fernando Caravaggio[a,b,*], Alexander J. Barnett[c], Shinichiro Nakajima[d], Yusuke Iwata[e], Julia Kim[a], Carol Borlido[a], Wanna Mar[a], Philip Gerretsen[a,b], Gary Remington[a,b], Ariel Graff-Guerrero[a,b]

[a] *Brain Health Imaging Centre, Centre for Addiction and Mental Health, 250 College Street, Toronto, ON M5T 1R8, Canada*
[b] *Department of Psychiatry, University of Toronto, 250 College Street, Toronto, ON M5T 1R8, Canada*
[c] *Center for Neuroscience, University of California, Davis, 1515 Newton Ct, Davis, California 95618, United States of America*
[d] *Department of Neuropsychiatry, Keio University, 2 Chome-15-45 Mita, Tokyo 108-8345, Japan*
[e] *Department of Neuropsychiatry, University of Yamanashi, 4 Chome-4-37 Takeda, Kofu 400-8510, Japan*

Received 29 July 2020; received in revised form 5 January 2022; accepted 10 January 2022

KEYWORDS
dopamine;
fMRI;
striatum

Abstract
Alpha-methyl-para-tyrosine (AMPT), a competitive inhibitor of tyrosine hydroxylase, can be used to deplete endogenous dopamine in humans. We examined how AMPT-induced dopamine depletion alters resting-state functional connectivity of the basal ganglia, and canonical resting-state networks, in healthy humans. Fourteen healthy participants (8 females; age [mean ± SD] = 27.93 ± 9.86) completed the study. Following dopamine depletion, the caudate showed reduced connectivity with the medial prefrontal cortex (mPFC) (Cohen's d = 1.89, p<.0001). Moreover, the caudate, putamen, globus pallidus, and midbrain all showed reduced connectivity with the occipital cortex (Cohen's d = 1.48-1.90; p<.0001-0.001). Notably, the dorsal caudate showed increased connectivity with the sensorimotor network (Co-

* Corresponding author.
E-mail address: fernando.caravaggio@camh.ca (F. Caravaggio).

https://doi.org/10.1016/j.euroneuro.2022.01.003

hen's $d = 2.03$, p=.002). AMPT significantly decreased self-reported motivation ($t(13)$=4.19, p=.001) and increased fatigue ($t(13)$=4.79, p=.0004). A greater increase in fatigue was associated with a greater reduction in connectivity between the substantia nigra and the mPFC (Cohen's $d = 3.02$, $p<.00001$), while decreased motivation was correlated with decreased connectivity between the VTA and left sensorimotor cortex (Cohen's $d = 2.03$, p=.00004). These findings help us to better understand the role of dopamine in basal ganglia function and may help us better understand neuropsychiatric diseases where abnormal dopamine levels are observed.

1. Introduction

The catecholamine neurotransmitter dopamine is involved in several key processes in the human brain, including reward motivation (Bloomfield et al., 2014; Caravaggio et al., 2018; Hofmans et al., 2020; Treadway et al., 2012) and cognitive and motor control (Brooks, 2001; Lappin et al., 2009; Strafella et al., 2003; Volkow et al., 1998). In particular, the afferent fibres of the midbrain dopamine system project to the striatum and prefrontal cortex. Abnormalities in the striatal dopamine system have been implicated in numerous psychiatric disorders, including Parkinson's disease (Kaasinen et al., 2019, 2021; Martini et al., 2018), addiction (Ashok et al., 2017; Caravaggio et al., 2021; Kamp et al., 2019; Proebstl et al., 2019), schizophrenia (Caravaggio et al., 2015b; Fusar-Poli and Meyer-Lindenberg, 2013; Kegeles et al., 2010), and attention-deficit hyperactivity disorder (Cherkasova et al., 2014; Fusar-Poli et al., 2012; Wu et al., 2012). Thus, understanding how alterations in dopamine affects brain function in humans may provide important insights into the future treatment of neuropsychiatric diseases.

Tyrosine hydroxylase, which catalyzes the conversion of L-tyrosine to levodopa, is the rate-limiting enzyme for catecholamine synthesis in the brain (Elsworth and Roth, 1997; Nagatsu et al., 1964). Alpha-methyl-para-tyrosine (AMPT; or metyrosine) is an amino acid analogue which competitively inhibits tyrosine hydroxylase (Engelman et al., 1968a; Spector et al., 1965). Using AMPT, it is possible to acutely deplete endogenous concentrations of dopamine and norepinephrine in humans over 24–48 h (Engelman and Sjoerdsma, 1966; Laruelle et al., 1997; Sjoerdsma et al., 1965). AMPT has been a useful tool for elucidating the contributions of dopamine and norepinephrine to human behavior and cognition (Bloemen et al., 2008; Booij et al., 2003; Ruhé et al., 2007; Verhoeff et al., 2003; Voruganti et al., 2001). Using AMPT in conjunction with positron emission tomography (PET) imaging has allowed for the quantification of endogenous dopamine in the striatum of healthy humans (Boot et al., 2008; Caravaggio et al., 2020, 2014; Cropley et al., 2008; Laruelle et al., 1997; Riccardi et al., 2008; Verhoeff et al., 2002, 2001) and persons with neuropsychiatric diseases (Abi-Dargham et al., 2000; Bloemen et al., 2013; Caravaggio et al., 2015b; Kegeles et al., 2010; Martinez et al., 2009).

However, the use of AMPT to investigate the effects of catecholamine depletion on resting-state functional connectivity of the human brain has yet to be explored. Functional magnetic resonance imaging (fMRI) studies exploring the role of dopamine depletion on brain function have used various depletion methods and outcome measures. Some fMRI studies have examined the effects of AMPT on task-dependent brain activation (da Silva Alves et al., 2013, 2011). Instead of AMPT, several fMRI studies have used a dietary dopamine depletion paradigm (Grevet et al., 2002; Leyton et al., 2004, 2000; McTavish et al., 1999; Montgomery et al., 2003; Palmour et al., 1998) to examine the effects of dopamine depletion on task-based activation (Bjork et al., 2014; Coull et al., 2012; Frank et al., 2016; Frey and McCabe, 2020; Nagano-Saito et al., 2012; Zebrowitz et al., 2018) and resting-state functional connectivity (Carbonell et al., 2014; Shafiei et al., 2019).

This dietary dopamine depletion paradigm involves having participants consume an amino acid beverage deficient in tyrosine and phenylalanine – often in conjunction with a low-protein diet (Badawy et al., 2010). Since tyrosine competes with other large neutral amino acids for entry through the blood-brain barrier (Fernstrom, 2005), this diet reduces the efficacy of tyrosine entry into the brain, reducing dopamine synthesis. Notably, this method requires the dietary depletion of the essential amino acid phenylalanine as well since tyrosine is synthesized in the liver from phenylalanine.

However, there are several potential limitations to the dietary dopamine depletion method (Badawy et al., 2010). First, the specificity and amount of tyrosine/phenylalanine depletion achieved across various studies with this method is often unclear (Badawy et al., 2010). Second, it is unclear how best to dose the dietary intervention to achieve similar levels of tyrosine/phenylalanine inhibition across subjects. Plasma levels of AMPT offer a reliable index of tyrosine hydroxylase inhibition and it is possible to achieve ~80% dopamine depletion across participants (Caravaggio et al., 2014; Engelman et al., 1968c; Laruelle et al., 1997). Finally, it is unclear if prior dietary habits or metabolic factors influence the efficacy of dietary dopamine depletion, with regards to abnormalities in baseline tyrosine/phenylalanine availability, dopamine synthesis, and blood-brain barrier function (Caravaggio et al., 2015a).

AMPT, although pharmacologically invasive, is the gold-standard for achieving acute and extensive (~80%) dopamine depletion in humans. Combined with PET imaging, AMPT has been an important tool for measuring striatal dopamine levels in humans. However, it is currently unknown how dopamine depletion with AMPT affects resting-state functional connectivity of the brain. Using resting-state fMRI, we explored how acute dopamine depletion with AMPT affects striatal connectivity, as well as canonical rest-

ing state networks, in healthy humans. We chose to specifically examine how dopamine depletion affects connectivity of the striatum as this region receives primary dopaminergic inputs from the midbrain. We believe these findings will help us to better understand the role of the dopaminergic system in regulating brain function. Moreover, this will help inform theoretical models of neuropsychiatric illness where dopaminergic abnormalities are associated with the disease pathophysiology.

2. Methods and materials

2.1. Participants

Twenty healthy participants (10 female; age [mean ± SD] = 28.5 ± 10.26) were enrolled in the study. One participant dropped out of the study prior to AMPT administration. Two participants dropped out of the study post AMPT, but prior to scanning, due to akathisia. Two participants dropped out during scanning due to feelings of claustrophobia/anxiety. Baseline fMRI data for one participant was unusable due to human error, and the subject's data was excluded from the study.

Fourteen healthy participants (8 female; age [mean ± SD] = 27.93 ± 9.86; Body mass index = 23.93 ± 2.85) completed the study. All participants were free of any major medical or psychiatric disorder as determined by clinical interview, the Mini-International Neuropsychiatric Interview, basic laboratory tests, and electrocardiogram. Participants were required to have a negative urine screen for drugs of abuse and/or pregnancy at inclusion and prior to each fMRI scan. All participants were non-smokers. The study was approved by the Research Ethics Board of the centre for Addiction and Mental Health (CAMH), Toronto, and no objection letter was issued by Health Canada. All participant recruitment took place at CAMH. All the participants provided written and informed consent.

2.2. AMPT administration

Dopamine depletion was induced by oral administration of 64 mg of AMPT per kilogram of body weight over 25 h. Independent of weight, no participant was dosed above 4500 mg, as per Health Canada Guidelines. AMPT was administered in six equal doses at the following times: 9:00am, 12:30pm (post 3.5 h), 5:00pm (post 8 h), and 9:00pm (post 12 h) on Visit 1, and 6:00am (post 21 h) and 10:00am (post 25 h) on Visit 2. The post AMPT MRI scan was scheduled at 12pm, 28 h after the initial dose of AMPT. Participants were kept under direct observation during AMPT administration and slept overnight on an inpatient unit at CAMH. This was done to monitor the safety of the participants and to ensure the AMPT dosing schedule was followed correctly. In addition, subjects were instructed to drink at least 4 L of fluids during the 2-day admission to prevent the formation of AMPT crystals in urine. Fluid intake was carefully monitored during the study to ensure compliance. Urine samples were collected at 2:00pm on Visit 1 and at 9:00am on Visit 2 to monitor AMPT crystals in urine. In addition, in order to alkalinize the urine, which increases AMPT solubility, sodium bicarbonate (1.25 g) was given orally at 10:00pm on the evening before Visit 1 and at 7am on Visit 1 of administration.

2.3. Plasma samples

Plasma levels of prolactin, homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenethyleneglycol (MHPG) were collected at 9:00am (Visit 1, prior to AMPT administration), 2:00pm (Visit 1) and 12:00pm (Visit 2). Plasma levels of AMPT were also collected at 2:00pm (Visit 1) and 12:00pm (Visit 2). Plasma prolactin, HVA, MHPG, and AMPT were quantified as previously described (Verhoeff et al., 2002). These plasma markers were chosen as they are indirect measures of endogenous dopamine levels – HVA and MHPG are metabolites of dopamine and norepinephrine, respectively, and dopamine inhibits the production of prolactin (Caravaggio et al., 2014).

2.4. Rating scales

Subjects were evaluated by the research psychiatrists (SN, PG, AG) for potential side effects at the following times: 9:00am (baseline), 2:00pm (post 5 hour dose), 12:00pm (post 27 hour dose), and at 3pm (post 30 hour dose). The presence of adverse effects such as parkinsonian symptoms, acute dystonia, and involuntary movements was monitored using the Simpson Angus Scale (SAS), Barnes Akathisia Scale (BAS), and the Global Assessment of Functioning (GAF) scale. To evaluate changes in energy, mood, and subjective well-being induced by dopamine depletion, the Profile of Mood States (POMS) and the Subjective Well-Being Under Neuroleptic Treatment (SWN) scale were administered.

2.5. MRI scanning

All participants were scanned at CAMH in a 3T GE Discovery MR750 scanner equipped with an eight-channel head coil. Participants had a three-dimensional inversion recovery-prepared T1-weighted MRI scan (BRAVO; GE Healthcare, Wauwatosa, WI) (echo time = 3.00 ms, repetition time (TR) = 6.74 ms, inversion time = 650 ms, flip angle = 8°, field of view = 230 mm, 256 × 256 matrix, slice thickness = 0.9 mm). Axial spiral resting-state scans were acquired for 6 min and 4 s (GRE/Fast GRE pulse sequence, slice thickness = 5 mm, TR = 2000; # of slices = 31, flip angle = 60°, field of view = 220 mm). Subjects were instructed to keep their eyes open during the scan.

2.6. Resting-state analysis

Prior to preprocessing, the timeseries from all subjects was visually inspected using fslview movie mode for any gross abnormalities. Preprocessing and analysis were performed using the CONN: functional connectivity toolbox version 17.a (https://www.nitrc.org/projects/conn/) (Whitfield-Gabrieli and Nieto-Castanon, 2012). The first three functional volumes of each run (Baseline and AMPT) were eliminated from the analysis to account for scanner stabilization. The images were reoriented to the anterior commissure and functional images were co-registered to the anatomical images before they were realigned and un-warped. The anatomical images were segmented into gray matter, white matter, and cerebral spinal fluid (CSF) and skull stripped. Normalization parameters from the segmentation were used to transform the functional and anatomical images into standard MNI space. Functional images were then smoothed using an 8 × 8 × 8 mm Gaussian kernel. Artifact detection toolbox was used to identify motion outliers. Thresholding was done according to the CONN "intermediate" default that flags timepoints with greater than 0.9 mm of composite motion and global signal outliers of greater than 5 standard deviations on a scan to scan basis to be flagged in outlier regressors. To account for physiological noise, a component based noise correction method (CompCor) (Behzadi et al., 2007) was used to regress out signal from the white matter and CSF and functional data was band-pass filtered between 0.008 – 0.09 Hz.

2.7. ROI analysis

We used the Harvard-Oxford subcortical atlases (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) to create an anatomical region of interest (ROI) for the left and right pallidum, caudate, putamen, and nucleus accumbens and we used a probabilistic atlas of the midbrain (Murty et al., 2014) to create ROIs for the ventral tegmental area (VTA) and substantia nigra (SN). We chose these ROIs (the basal ganglia) as these are the main dopaminergic regions. All ROIs were thresholded at 50% and are displayed in Supplementary Figure 1. For each run, the average signal from each ROI was correlated with every voxel in the brain after regressing out noise covariates. The resulting Pearson's correlation values were Fisher z-transformed. A within subject analysis was used to calculate the difference in connectivity between baseline and dopamine depletion. Mean centered percent change in POMS Fatigue and POMS Vigor were entered into the model as covariates of interest to explore voxel-wise changes in connectivity from baseline to depletion. Results were thresholded at a cluster threshold of $p<.05$, family wise error corrected.

2.8. Canonical resting network analysis

Using the CONN toolbox, group-ICA was performed to identify canonical resting state networks and interrogate the effect of dopamine depletion on these networks. A group-ICA was performed as per Calhoun et al. (Calhoun et al., 2005), with variance normalization pre-conditioning, subject-level dimensionality reduction, fastICA to estimate independent spatial components, and GICA1 to backproject the components to the individual-subject level. Networks were identified and labelled based on their similarity to canonical networks using a DICE coefficient. Components corresponding to the default mode, sensorimotor, salience, dorsal attention, frontoparietal, and cerebellar networks were used for within-subjects analysis to contrast baseline connectivity with dopamine depletion.

2.9. Statistical analyses

Statistical analyses were conducted using GraphPad (v.8.4.3; GraphPad Software, La Jolla, California). Normality of variables was determined using the D'Agostino-Pearson test. Where paired data were not normally distributed (e.g. complete absence of akathisia at baseline), the Wilcoxon matched-pairs sign rank test was employed. The significance level for all tests was set at $p<.05$ (two-tailed).

In total, we performed 25 contrasts of interest with fMRI (pre- and post- AMPT) which resulted in 30 t-test results (see Supplementary Table 3). We controlled for family-wise error (FWE) by correcting for multiple statistical contrasts using the Holm-Bonferroni method (see Supplementary Table 3). Notably, our within subjects design achieved 99%−100% power to detect all significant effects of interest (see Supplementary Table 3).

3. Results

3.1. Plasma changes

Plasma characteristics are presented in Supplementary Table 1. The average dose of AMPT administered was 4035.7(±671.23)mg. The average plasma concentration of AMPT after 27 h of oral administration was

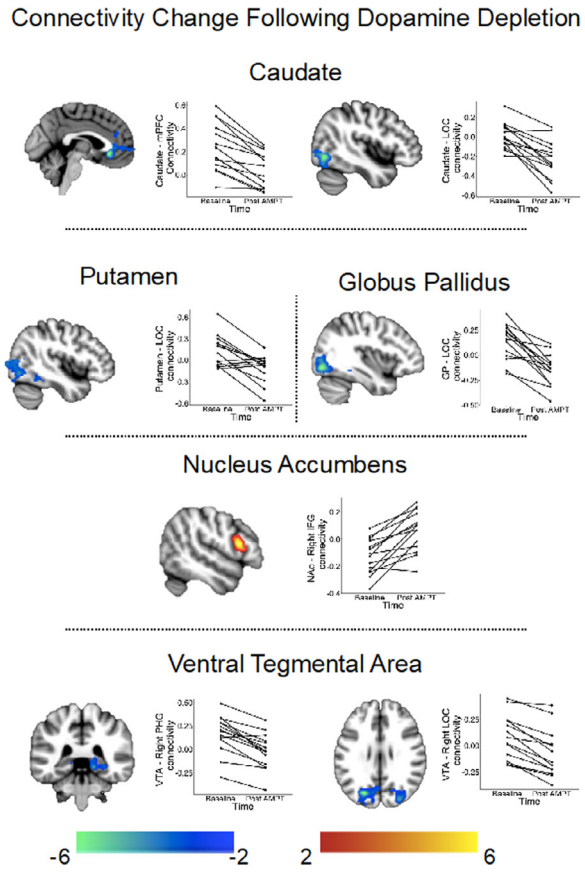

Fig. 1 Functional connectivity changes following dopamine depletion via AMPT presented on the MNI-152 brain with accompanying change plots for the peak coordinate in significant clusters. Each line represents a given subject. Voxelwise cluster changes are thresholded at $p < .05$ cluster corrected using FWE. (Abbreviations in Fig.: mPFC: medial prefrontal cortex; GP: globus pallidus; VTA: ventral tegmental area; IFG: inferior frontal gyrus; PHG: parahippocampal gyrus; LOC: lateral occipital cortex).

22.4(±7.44)μg/mL. Based on this average plasma concentration of AMPT, the average tyrosine hydroxylase inhibition in our sample can be estimated to be ∼80% (Engelman et al., 1968b; Laruelle et al., 1997; Udenfriend et al., 1965). This plasma level of AMPT was similar, and not significantly different from, that achieved by our previous PET study (24±11 μg/mL; $t(22)=0.43$, $p=.67$), which was associated with significant dopamine depletion in the striatum (Caravaggio et al., 2014).

Compared to baseline, plasma levels of prolactin were significantly increased after 5 h ($t(12)=9.31$, $p<.0001$) and 27 h ($t(13)=6.34$, $p<.0001$) of AMPT administration. Compared to baseline, plasma levels of HVA were significantly decreased after 5 h ($t(13)=5.00$, $p=.0002$) and 27 h ($t(13)=5.29$, $p=.0001$) of AMPT administration. Compared to baseline, plasma levels of MHPG were significantly decreased after 5 h ($t(13)=6.06$, $p<.0001$) and 27 h ($t(13)=10.48$, $p<.0001$) of AMPT administration.

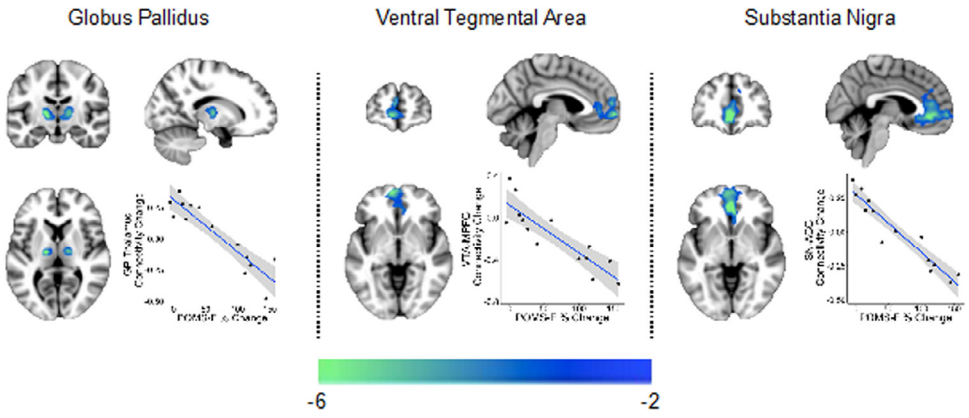

Fig. 2 Functional connectivity changes following dopamine depletion via AMPT associated with percent fatigue change measured by the POMS-F with accompanying scatterplot from the peak coordinate. Voxelwise cluster changes are thresholded at $p < .05$ cluster corrected using FWE. (Abbreviations in Fig.: mPFC: medial prefrontal cortex; GP: globus pallidus; VTA: ventral tegmental area; SN: substantia nigra).

3.2. Subjective changes

Subjective well-being, as measured by SWN total scores, significantly decreased at 27 h ($t(13)$=3.31, p=.006) but not at 5 h ($t(13)$=1.94, p=.07) after AMPT treatment (SWN Total Scores: Baseline: 102.9 ± 11.53; Post 5 h: 100.6 ± 11.41; Post 27 h: 89.29±17.03). The effect of AMPT on mood is presented in Supplementary Table 2. At 27 h, AMPT significantly increased fatigue measured by POMS-F ($t(13)$=4.79, p=.0004) and decreased motivation measured by POMS-V ($t(13)$=4.19, p=.001) compared to baseline.

3.3. Adverse events

The global functioning of participants, as assessed by the GAF, was significantly reduced after 5 h ($t(13)$=2.46, p=.03) and 27 h ($t(13)$=5.53, p<.0001) of AMPT administration (GAF Scores: Baseline: 99.64±1.34; Post 5 h: 97.14±4.26; Post 27 h 86.79±9.53). Parkinsonian symptoms, as assessed by the SAS, significantly increased compared to baseline after 27 h of AMPT administration ($W = 21$, p=.03). The increase in Parkinsonian symptoms did not reach significance post 5 h ($W = 1$, p>.99) (SAS Scores: Baseline: 0.14±0.53; Post 5 h: 0.21±0.58; Post 27 h: 0.57±0.65). Akathisia, assessed by the BAS, increased over the course of AMPT administration (BAS Scores: Baseline: 0; Post 5 h: 0.07±0.27; Post 27 h: 0.50±0.85). However, this increase in akathisia did not reach statistical significance (5 h: $W = 1$, p>.99; 27 h: $W = 10$, p=.13). Despite this, we note that several participants had clinically notable akathisia, and two participants dropped out due to significant akathisia. Urine testing revealed two participants developed significant crystalluria and were treated after their fMRI scan accordingly.

3.4. Region of interest results

Following dopamine depletion, we observed a reduction in connectivity from the caudate to medial prefrontal cortex (mPFC) (Cohen's $d = 1.89$, p=.0006). The caudate was functionally connected to the mPFC at baseline but had reduced connectivity following AMPT. Further, the caudate (Cohen's $d = 1.89$, p=.0006), putamen (Cohen's $d = 1.76$, p=.0002), and the globus pallidus (Cohen's $d = 1.90$, p=.00003) all showed reductions in connectivity to the right lateral occipital cortex (LOC). These regions were not reliably connected to the LOC at baseline, but following AMPT they became mildly anticorrelated with the LOC. These results survived FWE correction for multiple statistical contrasts (see Supplementary Table 3).

In the nucleus accumbens (NAc), we observed increased connectivity to the right inferior frontal gyrus (IFG) (Cohen's $d = 1.50$, p=.04). At baseline the NAc was anticorrelated with the right IFG and, following AMPT, the NAc lost this anticorrelation. However, this finding did not survive FWE correction for multiple statistical contrasts (see Supplementary Table 3). In the VTA we observed reduced connectivity to the thalamus, parahippocampus and hippocampus (Cohen's $d = 1.76$, p=.03), as well as the superior LOC (Cohen's $d = 1.48$, p=.00009). Thus, the VTA was connected to the thalamus, parahippocampus, and hippocampus at baseline, but lost this connectivity following dopamine depletion, while anticorrelations increased to the LOC. However, only connectivity changes with the superior LOC survived FWE correction for multiple statistical contrasts (see Supplementary Table 3). These findings are shown in Fig. 1 and the peak coordinates are found in Table 1.

When we investigated what connectivity changes were related to fatigue, we found a negative correlation between globus pallidus-thalamus connectivity change and percent change in fatigue (Cohen's $d = 2.20$, p=.02). Those individuals who showed a greater increase in fatigue, also saw a greater decrease in connectivity between the globus pallidus and the thalamus. These relationships did not survive FWE correction for multiple statistical comparisons (see Supplementary Table 3).

We also observed a negative correlation between VTA-mPFC connectivity with percent change in fatigue (Cohen's $d = 1.76$, p=.01), and a negative correlation between SN-mPFC connectivity with percent change in fatigue (Cohen's $d = 3.02$, p=.0000000001).The latter relationship survived

Table 1 Cluster regions, hemisphere, peak coordinates, test statistic, and cluster size for connectivity differences between baseline and dopamine depletion conditions.

Region	Hemisphere	Peak Coordinate			T	Cluster size (voxels)
		X	Y	Z		
Caudate connectivity						
anterior cingulate	B	0	28	−6	7.06	995
frontal pole	L	−12	64	−4	4.67	
LOC	R	44	−70	−6	6.33	898
Putamen connectivity						
LOC	R	48	−84	8	5.28	1408
Globus Pallidus connectivity						
LOC	R	40	−76	−8	7.12	1515
Occipital Fusiform	L	−30	−78	−12	6.4	683
Nucleus Accumbens connectivity						
IFG	R	54	16	14	5.6	554
VTA connectivity						
LOC	L	−22	−74	28	6.6	1168
PHG	R	16	−36	−6	6.47	573
Hippocampus	R	30	−42	−4	5.48	
Thalamus	R	10	−26	−2	4.92	
LOC	R	58	−64	−8	5.52	1263

Abbreviations: B, bilateral; IFG, inferior frontal gyrus; L, left; LOC, lateral occipital cortex; PHG, parahippocampal gyrus; R, right; VTA, ventral tegmental area. Coordinates are presented in MNI space.

Table 2 Cluster regions, hemisphere, peak coordinates, test statistic, and cluster size for connectivity correlations with POMS-F, a measure of fatigue.

Region	Hemisphere	Peak Coordinate			T	Cluster size (voxels)
		X	Y	Z		
Globus Pallidus Connectivity						
Thalamus	L	−16	−14	6	7.94	650
Thalamus	R	16	−14	6	5.42	
VTA connectivity						
medial prefrontal BA10	B	−8	60	−4	6.34	1080
Substantia Nigra Connectivity						
Paracingulate gyrus	B	−2	42	−6	10.91	2502
anterior cingulate	B	−4	32	8	6.01	
medial prefrontal BA10	B	−4	60	−4	5.92	
LOC	R	60	−66	14	6.81	422

Abbreviations: B, bilateral; BA, Brodmann area; L, left; LOC, lateral occipital cortex; R, right; VTA, ventral tegmental area. Coordinates are presented in MNI space.

FWE correction for multiple statistical comparisons (see Supplementary Table 3). Thus, individuals who showed a greater increase in fatigue, also had greater reductions in connectivity between midbrain dopaminergic regions with the mPFC. These results are shown in Fig. 2 and peak coordinates are reported in Table 2.

When we investigated the connectivity changes that were related to motivation, we found a positive correlation between motivation change and connectivity change between the VTA and sensorimotor cortex (Cohen's $d = 2.03$, p=.00004). This relationship survived FWE correction for multiple statistical comparisons (see Supplementary Table 3). Thus, individuals who had a reduction in motivation, also had a relatively greater reduction in connectivity between the VTA and left sensorimotor cortex. No other connectivity changes were related to motivation change. These results are shown in Fig. 3.

3.5. Canonical resting network analysis

We were able to identify 8 components from the group ICA and they were labelled according to their spatial match with CONN toolbox canonical networks as defined from CONN's ICA analyses of Human Connectome Project dataset of 497 subjects. Best spatial match was determined via DICE coefficient. These components corresponded to the default mode, sensorimotor, visual, salience, dorsal attention, frontoparietal, language and cerebellar network. Of interest, we examined the default mode, sensorimotor, salience, dor-

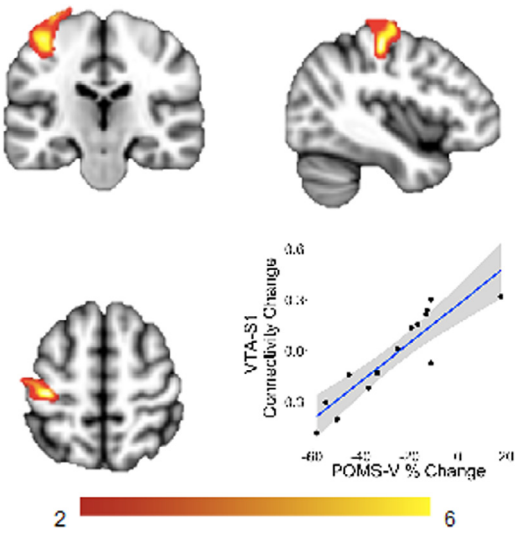

Fig. 3 Functional connectivity change following dopamine depletion via AMPT associated with percent motivation change measured by the POMS-V with accompanying scatterplot from the peak coordinate. Voxelwise cluster changes are thresholded at $p < .05$ cluster corrected using FWE. Peak coordinate: $x = -44$, $y = -16$, $z = 64$, $t = 7.33$; cluster size = 570 voxels. (Abbreviations in Fig.: VTA: ventral tegmental area; IFG: inferior frontal gyrus; S1: primary somatosensory cortex).

sal attention, frontoparietal, and cerebellar networks and found differences only in the sensorimotor network. The sensorimotor network had increased connectivity to the left dorsal striatum (Cohen's $d = 2.03$, p=.002;peak $x = -10$, $y = 4$, $z = 16$, $T = 7.58$, cluster size = 601) following dopamine depletion (Supplementary Fig. 2). This relationship survived FWE correction for multiple statistical comparisons (see Supplementary Table 3).

4. Discussion

Our study examined the effects of acute dopamine depletion with AMPT on resting-state functional connectivity in the brain. First, we conducted ROI based analyses exploring how dopamine depletion affected the connectivity of the basal ganglia with the rest of the brain. Dopamine depletion reduced connectivity between the caudate and mPFC. This is consistent with the known anatomical and topographical projections of the mPFC to the caudate (Alexander et al., 1986; Cho et al., 2015; Parent and Hazrati, 1995; Purves, 2001; Strafella et al., 2001; Yin et al., 2008), and previous functional connectivity studies (Choi et al., 2012; Di Martino et al., 2008; Draganski et al., 2008; Tziortzi et al., 2013, 2014). Our data further supports the important role of dopamine signaling in the caudate as an important modulator of mPFC-dependent activity and cognition (Cropley et al., 2006; Jokinen et al., 2009; Niethammer et al., 2013; Rajji et al., 2017).

AMPT-induced dopamine depletion also decreased connectivity between several regions (caudate, putamen, globus pallidus, and the VTA) with the LOC. While the primary visual cortex does not project to the striatum (Purves, 2001), there are projections from the LOC to the striatum (Purves, 2001; Tziortzi et al., 2013, 2014; Zhang and Li, 2018). It has been estimated that projections from the occipital lobe may represent 2% of the total afferent projections to the striatum (by striatal volume) (Tziortzi et al., 2013). Some fMRI studies suggest that activity in the ventral striatum, midbrain, sensorimotor cortex, and visual cortex may positively scale with motivation (Kohli et al., 2018). Interestingly, amphetamine and cocaine, which increases striatal dopamine, may increase the connectivity between the striatum and occipital cortex (Manza et al., 2019; Zhang and Li, 2018). In patients with schizophrenia, motivational deficits have been related to reduced connectivity between the VTA and the right LOC – among other regions (Giordano et al., 2018). Moreover, several studies have highlighted the interplay between striatal dopamine and the occipital cortex, particularly in the context of modulating visual perception to reward cues and incentive salience (Arsenault et al., 2013). It is plausible that changes in dopaminergic-based motivational states can affect perception and perceptual judgements in humans (Balcetis, 2015). Future studies should examine how changes in striatal dopamine levels in humans are related to changes in the perception of reward cues and incentive stimuli as a function of occipital connectivity to the basal ganglia.

We replicated previous findings that AMPT significantly increased fatigue and decreased motivation as measured by the POMS (Caravaggio et al., 2014; Verhoeff et al., 2002, 2003). Thus, our correlational analyses focused on these AMPT-induced subjective changes. We observed that AMPT-induced decreases in motivation were associated with decreases in connectivity between the midbrain (VTA) and the left sensorimotor cortex. This is consistent with previous findings that activity in both of these regions is associated with greater motivation (Kohli et al., 2018), and is generally consistent with the role of dopamine in increasing motivated motor actions (Caravaggio et al., 2018; Treadway et al., 2012). Moreover, we observed that AMPT-induced fatigue was associated with decreased connectivity between the substantia nigra and the mPFC/paracingulate gyrus. More human research is required to disentangle the unique contributions of midbrain dopamine and frontal cortical regions to motivation versus fatigue/arousal in general.

Examining changes in canonical resting-state connectivity networks, we found dopamine depletion specifically increased connectivity between the sensorimotor network and the left dorsal striatum, particularly the caudate. While unclear, this may represent a compensatory mechanism to maintain fine motor control under dopamine depletion. In support of this idea, early stage, minimally treated patients with Parkinson's disease show connectivity between the caudate and supplementary motor areas which is not present in healthy controls (Sang et al., 2015). Future studies are needed to determine how changes in sensorimotor network connectivity is associated with changes in motivation and cognition under dopamine depletion.

Collectively, our findings help us to better understand the classical model of the basal ganglia and the role dopamine in modulating brain function. These findings may help to inform theoretical models of neuropsychiatric disease where

abnormalities in striatal dopamine are thought to play a role in the pathophysiology. For example, it has been demonstrated that patients with schizophrenia have increased endogenous dopamine in the caudate (Abi-Dargham et al., 2000; Caravaggio et al., 2015b; Kegeles et al., 2010) as well as functional, anatomical, and neurochemical abnormalities in the anterior cingulate cortex (Egerton et al., 2012; Iwata et al., 2019; Kegeles et al., 2012; Reid et al., 2010; Smesny et al., 2015). We found dopamine depletion decreased connectivity between the caudate and the anterior cingulate cortex/mPFC. Future PET studies should examine whether endogenous dopamine levels in the caudate of patients with schizophrenia is correlated with its connectivity to the mPFC, and in turn, the severity of self-monitoring deficits and auditory hallucinations (Carter et al., 2001; Sapara et al., 2015).

There are several limitations to the current investigation. First, we did not employ an active placebo condition. This was not done due to technical and ethical considerations. However, even if a placebo condition were employed, it is unlikely participants would not be able to deduce the AMPT condition, given the severity of effects AMPT produces. Second, our sample is a uniquely self-selecting group; namely, individuals who can tolerate AMPT administration over 27 h. Third, dopamine depletion also depletes endogenous norepinephrine concentrations. Thus, the unique effect of norepinephrine depletion is unknown. However, these limitations are shared by all brain imaging studies employing AMPT. Finally, we administered AMPT over 24+ hours rather than 48 h, as in some studies (Abi-Dargham et al., 2000; Kegeles et al., 2010; Laruelle et al., 1997; Martinez et al., 2009). However, since inhibition of tyrosine hydroxylase is saturable and non-linear (i.e., plasma AMPT levels ranging from 20 to 30 μg/mL results in roughly the same 80% inhibition) (Laruelle et al., 1997; Udenfriend et al., 1965), the benefits of 48 hour depletion (especially in the context of potentially higher dropout rates) is unclear. Our meta-analysis of AMPT PET studies suggests that, while variability is improved, there is no statistically significant difference in dopamine depletion achieved between 24+ hours and 48 h of AMPT dosing (Caravaggio et al., 2020).

In conclusion, AMPT causes significant reductions in connectivity between several cortical regions and the basal ganglia. This dysconnectivity was generally correlated with increases in fatigue and decreases in motivation. However, dopamine depletion also increased the connectivity between the striatum and the sensorimotor network. Future studies are necessary to elucidate the cognitive and behavioural consequences of these changes. While AMPT studies are difficult to conduct, given our emphasis on ROI and canonical network-based analyses, our work is highly amenable to replication by future studies. We believe this work will help inform the role of dopamine in basal ganglia function and neuropsychiatric diseases.

5. Contributors

Dr. Fernando Caravaggio contributed to the study design, as well as the acquisition, analysis, and interpretation of the data. Dr. Alex Barnett contributed to the analysis and interpretation of the data. Dr. Shinichiro Nakajima contributed to the acquisition, analysis, and interpretation of the data. Dr. Yusuke Iwata contributed to the analysis and interpretation of the data. Ms. Julia Kim contributed to the analysis and interpretation of the data. Ms. Carol Borlido and Ms. Wanna Mar contributed to the acquisition of the data. Dr. Philip Gerretsen and Dr. Gary Remington contributed to the interpretation of the data. Dr. Ariel Graff-Guerrero contributed to the study design, as well as the acquisition, analysis, and interpretation of the data. All authors aided in the drafting, editing, and revising of the manuscript

Role of funding source

This study was funded by the Canadian Institutes of Health Research (CIHR) (MOP-114,989) and US National Institutes of Health (NIH) (RO1MH084886-01A2). The CIHR and the NIH had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Declaration of Competing Interest

The authors declare no financial conflicts of interest related to the study.

Acknowledgments

We would like to thank all the subjects who participated in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.01.003.

References

Abi-Dargham, A., Rodenhiser, J., Printz, D., Zea-Ponce, Y., Gil, R., Kegeles, L.S., Weiss, R., Cooper, T.B., Mann, J.J., Van Heertum, R.L., 2000. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc. Natl. Acad. Sci. 97, 8104–8109.

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Arsenault, J.T., Nelissen, K., Jarraya, B., Vanduffel, W., 2013. Dopaminergic reward signals selectively decrease fMRI activity in primate visual cortex. Neuron 77, 1174–1186.

Ashok, A.H., Mizuno, Y., Volkow, N.D., Howes, O.D., 2017. Association of stimulant use with dopaminergic alterations in users of cocaine, amphetamine, or methamphetamine: a systematic review and meta-analysis. JAMA Psychiatry 74, 511–519.

Badawy, A.A.-B., Dougherty, D.M., Richard, D.M., 2010. Specificity of the acute tryptophan and tyrosine plus phenylalanine depletion and loading tests I. Review of biochemical aspects and poor specificity of current amino acid formulations. Int. J. Tryptophan Res. 3, IJTR S5134.

Balcetis, E., 2015. Approach and avoidance as organizing structures for motivated distance perception. Emotion Rev. 8, 115–128.
Behzadi, Y., Restom, K., Liau, J., Liu, T.T., 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 37, 90–101.
Bjork, J.M., Grant, S.J., Chen, G., Hommer, D.W., 2014. Dietary tyrosine/phenylalanine depletion effects on behavioral and brain signatures of human motivational processing. Neuropsychopharmacology 39, 595–604.
Bloemen, O.J., De Koning, M., Boot, E., Booij, J., van Amelsvoort, T., 2008. Challenge and therapeutic studies using alpha-methyl-para-tyrosine (AMPT) in neuropsychiatric disorders: a review. Central Nervous Syst. Agents Med. Chem. (Formerly Current Medicinal Chemistry-Central Nervous System Agents) 8, 249–256.
Bloemen, O.J., de Koning, M.B., Gleich, T., Meijer, J., de Haan, L., Linszen, D.H., Booij, J., van Amelsvoort, T.A., 2013. Striatal dopamine D2/3 receptor binding following dopamine depletion in subjects at ultra high risk for psychosis. Eur. Neuropsychopharmacol. 23, 126–132.
Bloomfield, M.A., Morgan, C.J., Kapur, S., Curran, H.V., Howes, O.D., 2014. The link between dopamine function and apathy in cannabis users: an [18 F]-DOPA PET imaging study. Psychopharmacology (Berl.) 231, 2251–2259.
Booij, L., Van der Does, A., Riedel, W., 2003. Monoamine depletion in psychiatric and healthy populations. Mol. Psychiatry 8, 951–973.
Boot, E., Booij, J., Hasler, G., Zinkstok, J.R., de Haan, L., Linszen, D.H., van Amelsvoort, T.A., 2008. AMPT-induced monoamine depletion in humans: evaluation of two alternative [123 I] IBZM SPECT procedures. Eur. J. Nucl. Med. Mol. Imaging 35, 1350–1356.
Brooks, D., 2001. Functional imaging studies on dopamine and motor control. J. Neural Transm. 108, 1283–1298.
Calhoun, V.D., Adali, T., Stevens, M., Kiehl, K., Pekar, J.J., 2005. Semi-blind ICA of fMRI: a method for utilizing hypothesis-derived time courses in a spatial ICA analysis. Neuroimage 25, 527–538.
Caravaggio, F., Borlido, C., Hahn, M., Feng, Z., Fervaha, G., Gerretsen, P., Nakajima, S., Plitman, E., Chung, J.K., Iwata, Y., 2015a. Reduced insulin sensitivity is related to less endogenous dopamine at D2/3 receptors in the ventral striatum of healthy nonobese humans. Int. J. Neuropsychopharmacolog. 18.
Caravaggio, F., Borlido, C., Wilson, A., Graff-Guerrero, A., 2015b. Examining endogenous dopamine in treated schizophrenia using [11C]-(+)-PHNO positron emission tomography: a pilot study. Clin. Chim. Acta 449, 60–62.
Caravaggio, F., Fervaha, G., Browne, C.J., Gerretsen, P., Remington, G., Graff-Guerrero, A., 2018. Reward motivation in humans and its relationship to dopamine D2/3 receptor availability: a pilot study with dual [11C]-raclopride and [11C]-(+)-PHNO imaging. J. Psychopharmacol. 32, 357–366.
Caravaggio, F., Iwata, Y., Kim, J., Shah, P., Gerretsen, P., Remington, G., Graff-Guerrero, A., 2020. What proportion of striatal D2 receptors are occupied by endogenous dopamine at baseline? A meta-analysis with implications for understanding antipsychotic occupancy. Neuropharmacology 163, 107591.
Caravaggio, F., Nakajima, S., Borlido, C., Remington, G., Gerretsen, P., Wilson, A., Houle, S., Menon, M., Mamo, D., Graff-Guerrero, A., 2014. Estimating endogenous dopamine levels at D 2 and D 3 receptors in humans using the agonist radiotracer [11 C]-(+)-PHNO. Neuropsychopharmacology 39, 2769–2776.
Caravaggio, F., Porco, N., Kim, J., Torres-Carmona, E., Brown, E., Iwata, Y., Nakajima, S., Gerretsen, P., Remington, G., Graff-Guerrero, A., 2021. Measuring amphetamine-induced dopamine release in humans: a comparative meta-analysis of [(11) C]-raclopride and [(11) C]-(+)-PHNO studies. Synapse 75, e22195.
Carbonell, F., Nagano-Saito, A., Leyton, M., Cisek, P., Benkelfat, C., He, Y., Dagher, A., 2014. Dopamine precursor depletion impairs structure and efficiency of resting state brain functional networks. Neuropharmacology 84, 90–100.
Carter, C.S., MacDonald III, A.W., Ross, L.L., Stenger, V.A., 2001. Anterior cingulate cortex activity and impaired self-monitoring of performance in patients with schizophrenia: an event-related fMRI study. Am. J. Psychiatry 158, 1423–1428.
Cherkasova, M.V., Faridi, N., Casey, K.F., O'driscoll, G.A., Hechtman, L., Joober, R., Baker, G.B., Palmer, J., Dagher, A., Leyton, M., 2014. Amphetamine-induced dopamine release and neurocognitive function in treatment-naive adults with ADHD. Neuropsychopharmacology 39, 1498–1507.
Cho, S.S., Koshimori, Y., Aminian, K., Obeso, I., Rusjan, P., Lang, A.E., Daskalakis, Z.J., Houle, S., Strafella, A.P., 2015. Investing in the future: stimulation of the medial prefrontal cortex reduces discounting of delayed rewards. Neuropsychopharmacology 40, 546–553.
Choi, E.Y., Yeo, B.T., Buckner, R.L., 2012. The organization of the human striatum estimated by intrinsic functional connectivity. J. Neurophysiol. 108, 2242–2263.
Coull, J.T., Hwang, H.J., Leyton, M., Dagher, A., 2012. Dopamine precursor depletion impairs timing in healthy volunteers by attenuating activity in putamen and supplementary motor area. J. Neurosci. 32, 16704–16715.
Cropley, V.L., Fujita, M., Innis, R.B., Nathan, P.J., 2006. Molecular Imaging of the Dopaminergic System and its Association with Human Cognitive Function. Biol. Psychiatry 59, 898–907.
Cropley, V.L., Innis, R.B., Nathan, P.J., Brown, A.K., Sangare, J.L., Lerner, A., Ryu, Y.H., Sprague, K.E., Pike, V.W., Fujita, M., 2008. Small effect of dopamine release and no effect of dopamine depletion on [18F] fallypride binding in healthy humans. Synapse 62, 399–408.
da Silva Alves, F., Bakker, G., Schmitz, N., Abeling, N., Hasler, G., van der Meer, J., Nederveen, A., de Haan, L., Linszen, D., van Amelsvoort, T., 2013. Dopaminergic modulation of the reward system in schizophrenia: a placebo-controlled dopamine depletion fMRI study. Eur. Neuropsychopharmacol. 23, 1577–1586.
da Silva Alves, F., Schmitz, N., Figee, M., Abeling, N., Hasler, G., van der Meer, J., Nederveen, A., de Haan, L., Linszen, D., van Amelsvoort, T., 2011. Dopaminergic modulation of the human reward system: a placebo-controlled dopamine depletion fMRI study. J. Psychopharmacol. 25, 538–549.
Di Martino, A., Scheres, A., Margulies, D.S., Kelly, A., Uddin, L.Q., Shehzad, Z., Biswal, B., Walters, J.R., Castellanos, F.X., Milham, M.P., 2008. Functional connectivity of human striatum: a resting state FMRI study. Cereb. Cortex 18, 2735–2747.
Draganski, B., Kherif, F., Klöppel, S., Cook, P.A., Alexander, D.C., Parker, G.J., Deichmann, R., Ashburner, J., Frackowiak, R.S., 2008. Evidence for segregated and integrative connectivity patterns in the human basal ganglia. J. Neurosci. 28, 7143–7152.
Egerton, A., Brugger, S., Raffin, M., Barker, G.J., Lythgoe, D.J., McGuire, P.K., Stone, J.M., 2012. Anterior cingulate glutamate levels related to clinical status following treatment in first-episode schizophrenia. Neuropsychopharmacology 37, 2515–2521.
Elsworth, J.D., Roth, R.H., 1997. Dopamine synthesis, uptake, metabolism, and receptors: relevance to gene therapy of Parkinson's disease. Exp. Neurol. 144, 4–9.
Engelman, K., Horwitz, D., Jéquier, E., Sjoerdsma, A., 1968a. Biochemical and pharmacologic effects of α-methyltyrosine in man. J. Clin. Invest. 47, 577–594.
Engelman, K., Jequier, E., Udenfriend, S., Sjoerdsma, A., 1968b. Metabolism of alpha-methyltyrosine in man: relationship to its potency as an inhibitor of catecholamine biosynthesis. J Clin Invest 47, 568–576.
Engelman, K., Jéquier, E., Udenfriend, S., Sjoerdsma, A., 1968c. Metabolism of α-methyltyrosine in man: relationship to its po-

tency as an inhibitor of catecholamine biosynthesis. J. Clin. Invest. 47, 568–576.
Engelman, K., Sjoerdsma, A., 1966. Inhibition of catecholamine biosynthesis in man. Circ. Res. 18 I-104-I-109.
Fernstrom, J.D., 2005. Branched-chain amino acids and brain function. J. Nutr. 135, 1539S–1546S.
Frank, S., Veit, R., Sauer, H., Enck, P., Friederich, H.-.C., Unholzer, T., Bauer, U.-.M., Linder, K., Heni, M., Fritsche, A., 2016. Dopamine depletion reduces food-related reward activity independent of BMI. Neuropsychopharmacology 41, 1551–1559.
Frey, A.-.L., McCabe, C., 2020. Effects of serotonin and dopamine depletion on neural prediction computations during social learning. Neuropsychopharmacology 1–7.
Fusar-Poli, P., Meyer-Lindenberg, A., 2013. Striatal presynaptic dopamine in schizophrenia, Part II: meta-analysis of [18F/11C]-DOPA PET studies. Schizophr Bull 39, 33–42.
Fusar-Poli, P., Rubia, K., Rossi, G., Sartori, G., Balottin, U., 2012. Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. Am. J. Psychiatry 169, 264–272.
Giordano, G.M., Stanziano, M., Papa, M., Mucci, A., Prinster, A., Soricelli, A., Galderisi, S., 2018. Functional connectivity of the ventral tegmental area and avolition in subjects with schizophrenia: a resting state functional MRI study. Eur. Neuropsychopharmacol. 28, 589–602.
Grevet, E.H., Tietzmann, M.R., Shansis, F.M., Hastenpflug, C., Santana, L.C., Forster, L., Kapczinski, F., Izquierdo, I., 2002. Behavioural effects of acute phenylalanine and tyrosine depletion in healthy male volunteers. J. Psychopharmacol. 16, 51–55.
Hofmans, L., Papadopetraki, D., van den Bosch, R., Määttä, J.I., Froböse, M.I., Zandbelt, B.B., Westbrook, A., Verkes, R.-.J., Cools, R., 2020. Methylphenidate boosts choices of mental labor over leisure depending on striatal dopamine synthesis capacity. Neuropsychopharmacology 45, 2170–2179.
Iwata, Y., Nakajima, S., Plitman, E., Caravaggio, F., Kim, J., Shah, P., Mar, W., Chavez, S., De Luca, V., Mimura, M., Remington, G., Gerretsen, P., Graff-Guerrero, A., 2019. Glutamatergic Neurometabolite Levels in Patients With Ultra-Treatment-Resistant Schizophrenia: a Cross-Sectional 3T Proton Magnetic Resonance Spectroscopy Study. Biol. Psychiatry 85, 596–605.
Jokinen, P., Brück, A., Aalto, S., Forsback, S., Parkkola, R., Rinne, J.O., 2009. Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy. Parkinsonism Relat. Disord. 15, 88–93.
Kaasinen, V., Kankare, T., Joutsa, J., Vahlberg, T., 2019. Presynaptic striatal dopaminergic function in atypical parkinsonism: a Metaanalysis of imaging studies. J. Nucl. Med. 60, 1757–1763.
Kaasinen, V., Vahlberg, T., Stoessl, A.J., Strafella, A.P., Antonini, A., 2021. Dopamine receptors in parkinson's disease: a meta-analysis of imaging studies. Mov. Disord..
Kamp, F., Proebstl, L., Penzel, N., Adorjan, K., Ilankovic, A., Pogarell, O., Koller, G., Soyka, M., Falkai, P., Koutsouleris, N., 2019. Effects of sedative drug use on the dopamine system: a systematic review and meta-analysis of in vivo neuroimaging studies. Neuropsychopharmacology 44, 660–667.
Kegeles, L.S., Abi-Dargham, A., Frankle, W.G., Gil, R., Cooper, T.B., Slifstein, M., Hwang, D.-.R., Huang, Y., Haber, S.N., Laruelle, M., 2010. Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. Arch. Gen. Psychiatry 67, 231–239.
Kegeles, L.S., Mao, X., Stanford, A.D., Girgis, R., Ojeil, N., Xu, X., Gil, R., Slifstein, M., Abi-Dargham, A., Lisanby, S.H., 2012. Elevated prefrontal cortex γ-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. Arch. Gen. Psychiatry 69, 449–459.
Kohli, A., Blitzer, D.N., Lefco, R.W., Barter, J.W., Haynes, M.R., Colalillo, S.A., Ly, M., Zink, C.F., 2018. Using Expectancy Theory to quantitatively dissociate the neural representation of motivation from its influential factors in the human brain: an fMRI study. Neuroimage 178, 552–561.
Lappin, J.M., Reeves, S.J., Mehta, M.A., Egerton, A., Coulson, M., Grasby, P.M., 2009. Dopamine release in the human striatum: motor and cognitive tasks revisited. J. Cerebral Blood Flow Metabol. 29, 554–564.
Laruelle, M., D'Souza, C.D., Baldwin, R.M., Abi-Dargham, A., Kanes, S.J., Fingado, C.L., Seibyl, J.P., Zoghbi, S.S., Bowers, M.B., Jatlow, P., Charney, D.S., Innis, R.B., 1997. Imaging D2 receptor occupancy by endogenous dopamine in humans. Neuropsychopharmacology 17, 162–174.
Leyton, M., Dagher, A., Boileau, I., Casey, K., Baker, G.B., Diksic, M., Gunn, R., Young, S.N., Benkelfat, C., 2004. Decreasing amphetamine-induced dopamine release by acute phenylalanine/tyrosine depletion: a PET/[11 C] raclopride study in healthy men. Neuropsychopharmacology 29, 427–432.
Leyton, M., Young, S.N., Pihl, R., Etezadi, S., Lauze, C., Blier, P., Baker, G., Benkelfat, C., 2000. Effects on mood of acute phenylalanine/tyrosine depletion in healthy women. Neuropsychopharmacology 22, 52–63.
Manza, P., Tomasi, D., Yuan, K., Kojori, E.S., Wiers, C., McFarland, M., Burns, J., Kroll, D., Feldman, D., McPherson, K., 2019. How dopamine release alters human brain networks: insights from simultaneous PET-fMRI, Neuropsychopharmacology. In: Nature Publishing Group Macmillan Building, 4 CRINAN ST, LONDON N1 9XW. ENGLAND, p. 222 -222.
Martinez, D., Greene, K., Broft, A., Kumar, D., Liu, F., Narendran, R., Slifstein, M., Van Heertum, R., Kleber, H.D., 2009. Lower level of endogenous dopamine in patients with cocaine dependence: findings from PET imaging of D 2/D 3 receptors following acute dopamine depletion. Am. J. Psychiatry 166, 1170–1177.
Martini, A., Dal Lago, D., Edelstyn, N.M., Salgarello, M., Lugoboni, F., Tamburin, S., 2018. Dopaminergic neurotransmission in patients with Parkinson's disease and impulse control disorders: a systematic review and meta-analysis of PET and SPECT studies. Front. Neurol. 9, 1018.
McTavish, S.F., Cowen, P.J., Sharp, T., 1999. Effect of a tyrosine-free amino acid mixture on regional brain catecholamine synthesis and release. Psychopharmacology (Berl.) 141, 182–188.
Montgomery, A.J., McTavish, S.F., Cowen, P.J., Grasby, P.M., 2003. Reduction of brain dopamine concentration with dietary tyrosine plus phenylalanine depletion: an [11C] raclopride PET study. Am. J. Psychiatry 160, 1887–1889.
Murty, V.P., Shermohammed, M., Smith, D.V., Carter, R.M., Huettel, S.A., Adcock, R.A., 2014. Resting state networks distinguish human ventral tegmental area from substantia nigra. Neuroimage 100, 580–589.
Nagano-Saito, A., Cisek, P., Perna, A.S., Shirdel, F.Z., Benkelfat, C., Leyton, M., Dagher, A., 2012. From anticipation to action, the role of dopamine in perceptual decision making: an fMRI-tyrosine depletion study. J. Neurophysiol. 108, 501–512.
Nagatsu, T., Levitt, M., Udenfriend, S., 1964. Tyrosine hydroxylase the initial step in norepinephrine biosynthesis. J. Biol. Chem. 239, 2910–2917.
Niethammer, M., Tang, C.C., Ma, Y., Mattis, P.J., Ko, J.H., Dhawan, V., Eidelberg, D., 2013. Parkinson's disease cognitive network correlates with caudate dopamine. Neuroimage 78, 204–209.
Palmour, R.M., Ervin, F.R., Baker, G.B., Young, S.N., 1998. An amino acid mixture deficient in phenylalanine and tyrosine reduces cerebrospinal fluid catecholamine metabolites and alcohol consumption in vervet monkeys. Psychopharmacology (Berl.) 136, 1–7.

Parent, A., Hazrati, .L..-N., 1995. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res. Rev. 20, 91–127.

Proebstl, L., Kamp, F., Manz, K., Krause, D., Adorjan, K., Pogarell, O., Koller, G., Soyka, M., Falkai, P., Kambeitz, J., 2019. Effects of stimulant drug use on the dopaminergic system: a systematic review and meta-analysis of in vivo neuroimaging studies. Eur. Psychiatry 59, 15–24.

Purves, D., 2001. Neuroscience, 2nd Edition Sunderland (MA) Sinauer Associates., Projections to the Basal Ganglia. Inc.

Rajji, T.K., Mulsant, B.H., Nakajima, S., Caravaggio, F., Suzuki, T., Uchida, H., Gerretsen, P., Mar, W., Pollock, B.G., Mamo, D.C., Graff-Guerrero, A., 2017. Cognition and Dopamine D2 Receptor Availability in the Striatum in Older Patients with Schizophrenia. Am. J. Geriatr. Psychiatry 25, 1–10.

Reid, M.A., Stoeckel, L.E., White, D.M., Avsar, K.B., Bolding, M.S., Akella, N.S., Knowlton, R.C., den Hollander, J.A., Lahti, A.C., 2010. Assessments of Function and Biochemistry of the Anterior Cingulate Cortex in Schizophrenia. Biol. Psychiatry 68, 625–633.

Riccardi, P., Baldwin, R., Salomon, R., Anderson, S., Ansari, M.S., Li, R., Dawant, B., Bauernfeind, A., Schmidt, D., Kessler, R., 2008. Estimation of baseline dopamine D2 receptor occupancy in striatum and extrastriatal regions in humans with positron emission tomography with [18F] fallypride. Biol. Psychiatry 63, 241–244.

Ruhé, H.G., Mason, N.S., Schene, A.H., 2007. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol. Psychiatry 12, 331–359.

Sang, L., Zhang, J., Wang, L., Zhang, J., Zhang, Y., Li, P., Wang, J., Qiu, M., 2015. Alteration of brain functional networks in early-stage Parkinson's disease: a resting-state fMRI study. PLoS One 10, e0141815.

Sapara, A., ffytche, D.H., Cooke, M.A., Williams, S.C.R., Kumari, V., 2015. Is it me? Verbal self-monitoring neural network and clinical insight in schizophrenia. Psychiatry Res. 234, 328–335.

Shafiei, G., Zeighami, Y., Clark, C.A., Coull, J.T., Nagano-Saito, A., Leyton, M., Dagher, A., Mišić, B., 2019. Dopamine signaling modulates the stability and integration of intrinsic brain networks. Cereb. Cortex 29, 397–409.

Sjoerdsma, A., Engelman, K., Spector, S., Udenfriend, S., 1965. Inhibition of catecholamine synthesis in man with alpha-methyltyrosine, an inhibitor of tyrosine hydroxylase. Lancet North Am. Ed. 286, 1092–1094.

Smesny, S., Gussew, A., Biesel, N.J., Schack, S., Walther, M., Rzanny, R., Milleit, B., Gaser, C., Sobanski, T., Schultz, C.C., Amminger, P., Hipler, U.-.C., Sauer, H., Reichenbach, J.R., 2015. Glutamatergic dysfunction linked to energy and membrane lipid metabolism in frontal and anterior cingulate cortices of never treated first-episode schizophrenia patients. Schizophr. Res. 168, 322–329.

Spector, S., Sjoerdsma, A., Udenfriend, S., 1965. Blockade of endogenous norepinephrine synthesis by α-methyl-tyrosine, an inhibitor of tyrosine hydroxylase. J. Pharmacol. Exp. Ther. 147, 86–95.

Strafella, A.P., Paus, T., Barrett, J., Dagher, A., 2001. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J. Neurosci. 21, RC157 -RC157.

Strafella, A.P., Paus, T., Fraraccio, M., Dagher, A., 2003. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain 126, 2609–2615.

Treadway, M.T., Buckholtz, J.W., Cowan, R.L., Woodward, N.D., Li, R., Ansari, M.S., Baldwin, R.M., Schwartzman, A.N., Kessler, R.M., Zald, D.H., 2012. Dopaminergic mechanisms of individual differences in human effort-based decision-making. J. Neurosci. 32, 6170–6176.

Tziortzi, A.C., Haber, S.N., Searle, G.E., Tsoumpas, C., Long, C.J., Shotbolt, P., Douaud, G., Jbabdi, S., Behrens, T.E.J., Rabiner, E.A., Jenkinson, M., Gunn, R.N., 2013. Connectivity-Based Functional Analysis of Dopamine Release in the Striatum Using Diffusion-Weighted MRI and Positron Emission Tomography. Cereb. Cortex 24, 1165–1177.

Tziortzi, A.C., Haber, S.N., Searle, G.E., Tsoumpas, C., Long, C.J., Shotbolt, P., Douaud, G., Jbabdi, S., Behrens, T.E.J., Rabiner, E.A., Jenkinson, M., Gunn, R.N., 2014. Connectivity-based functional analysis of dopamine release in the striatum using diffusion-weighted MRI and positron emission tomography. Cereb Cortex 24, 1165–1177.

Udenfriend, S., Zaltzman-Nirenberg, P., Nagatsu, T., 1965. Inhibitors of purified beef adrenal tyrosine hydroxylase. Biochem. Pharmacol. 14, 837–845.

Verhoeff, N., Hussey, D., Lee, M., Tauscher, J., Papatheodorou, G., Wilson, A., Houle, S., Kapur, S., 2002. Dopamine depletion results in increased neostriatal D 2, but not D 1, receptor binding in humans. Mol. Psychiatry 7, 322–328.

Verhoeff, N., Kapur, S., Hussey, D., Lee, M., Christensen, B., Psych, C., Papatheodorou, G., Zipursky, R., 2001. A simple method to measure baseline occupancy of neostriatal dopamine D2 receptors by dopamine in vivo in healthy subjects. Neuropsychopharmacology 25, 213–223.

Verhoeff, N.P.L.G., Christensen, B.K., Hussey, D., Lee, M., Papatheodorou, G., Kopala, L., Rui, Q., Zipursky, R.B., Kapur, S., 2003. Effects of catecholamine depletion on D2 receptor binding, mood, and attentiveness in humans: a replication study. Pharmacol. Biochem. Behav. 74, 425–432.

Volkow, N.D., Gur, R.C., Wang, G.-.J., Fowler, J.S., Moberg, P.J., Ding, Y.-.S., Hitzemann, R., Smith, G., Logan, J., 1998. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am. J. Psychiatry 155, 344–349.

Voruganti, L., Slomka, P., Zabel, P., Costa, G., So, A., Mattar, A., Awad, A.G., 2001. Subjective effects of AMPT-induced dopamine depletion in schizophrenia: correlation between dysphoric responses and striatal D2 binding ratios on SPECT imaging. Neuropsychopharmacology 25, 642–650.

Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2, 125–141.

Wu, J., Xiao, H., Sun, H., Zou, L., Zhu, .L..-Q., 2012. Role of dopamine receptors in ADHD: a systematic meta-analysis. Mol. Neurobiol. 45, 605–620.

Yin, H.H., Ostlund, S.B., Balleine, B.W., 2008. Reward-guided learning beyond dopamine in the nucleus accumbens: the integrative functions of cortico-basal ganglia networks. Eur. J. Neurosci. 28, 1437–1448.

Zebrowitz, L.A., Boshyan, J., Ward, N., Hanlin, L., Wolf, J.M., Hadjikhani, N., 2018. Dietary dopamine depletion blunts reward network sensitivity to face trustworthiness. J. Psychopharmacol. 32, 965–978.

Zhang, S., Li, C.-S.R., 2018. Ventral striatal dysfunction in cocaine dependence–difference mapping for subregional resting state functional connectivity. Transl. Psychiatry 8, 1–11.