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## **Lower midbrain dopamine transporter availability in depressed patients: Report from high-resolution PET imaging**

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## Abstract

**Background.** A reduced presynaptic dopamine neurotransmission has long been implicated in major depressive disorder (MDD). However, molecular imaging studies that assessed the dopamine transporter (DAT) availability have led to inconsistent results, partly due to methodological considerations, and to exclusive focus on the striatum, precluding findings in extra-striatal regions.

**Methods.** Herein, we leveraged our database of high-resolution Positron Emission Tomography (PET) images acquired with a highly selective radiotracer, [<sup>11</sup>C]PE2I, to assess striatal and extra-striatal DAT availability in eight patients treated for depression compared to twenty-four healthy controls.

**Results.** Statistical parametric mapping and voxel-based analyses of PET images detected a significant lower DAT availability in depressed patients within the superior part of the midbrain (right,  $p_{FWE} = 0.002$ ; left,  $p_{FWE} = 0.006$ ), a region including the ventral tegmental area and the substantia nigra from where the mesocorticolimbic and nigrostriatal dopamine pathways originate. A similar difference was found in the right dorsal putamen ( $p_{FWE} = 0.012$ ).

**Limitations.** The statistical power was limited to detect only large effects, due to the size of the patients' sample.

**Conclusions.** The findings support the hypothesis that a reduced presynaptic dopamine function plays a role in the pathophysiology of depression, and that extra-striatal dopamine function should be further investigated.

**Key words:** Depression, DAT, Neuroimaging, PET

## Introduction

A decreased dopamine (DA) neurotransmission has long been thought to be involved in the pathophysiology of depression (Dunlop and Nemeroff, 2007). Nonetheless, relatively few imaging studies did examine the dopaminergic system in the context of depression. Most focused on the DA transporter (DAT), a ubiquitous component of DA neurons regulating DA transmission (McHugh and Buckley, 2015), without achieving a consistent set of results (Camardese et al., 2014). Thus, a meta-analysis of 12 case-control imaging studies including 209 patients with depression and 314 healthy controls revealed no evidence for striatal DAT alteration in depression (Li et al., 2015). Yet, the difference of methodologies between the studies could account for the inconsistent results. Indeed, the poor spatial resolution of the scanners, the use of various tracers including non- or poorly specific radioligands (*e.g.*, [<sup>123</sup>I]β-CIT, [<sup>123</sup>I]nor-β-CIT, [<sup>123</sup>I]FP-CIT, [<sup>11</sup>C]RTI-32), and the various quantification methods represent important limitations in interpreting these data (Camardese et al., 2014). Moreover, previous imaging studies assessed the DAT within striatal ROIs exclusively, possibly precluding interesting results to be revealed in extra-striatal regions.

Thus, in order to provide additional data on this issue, we sought to determine whether striatal and extra-striatal DAT alterations could be detected in depressed patients using a voxel-based analysis of PET images acquired on a high-resolution research tomograph (HRRT) with [<sup>11</sup>C]PE2I, a potent and highly selective DAT radiotracer (Halldin et al., 2003). This tracer is particularly advantageous for PET examination of DAT availability in the midbrain, as it presents a favorable signal-to-noise ratio both in the human striatum and in midbrain regions (Jucaite et al., 2006). This analysis was conducted in a small sample of patients diagnosed with major depressive disorder (MDD) and a group of healthy controls, initially included in a wider PET and MRI database built in the team from 2005 to 2012 (Artiges et al., 2017; Dubol et al., 2018).

## Methods

*Participants:* Eight patients who met criteria for a diagnosis of MDD according to the DSM-IV-TR and twenty-four matched healthy controls were extracted from our database and included in the study. The MDD patients were recruited by senior psychiatrists from psychiatric departments of Central Paris and South Paris area. All patients were being

followed up on an ambulatory basis and were receiving antidepressant treatment (mg/day) in monotherapy, including fluoxetine (20, 30), paroxetine (40, 60), citalopram (20), venlafaxine (37.5, 187.5) and mirtazapine (22.5). No association with other psychotropic treatment was allowed, except low dosage of benzodiazepines. The patients were in a stabilized state with residual symptoms. On the day of examination, the severity of their depressive symptoms was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS). Additionally, all participants filled in the Beck Depression Inventory (BDI) and the Spielberg State-Trait Anxiety Inventory (STAI) auto-questionnaires. Exclusion criteria were: age over 60, any substance related Axis I disorder (except tobacco dependence) in the past six months, treatment susceptible to interfere directly with DAT, electroconvulsive therapy (ECT) treatment in the past six months, any present medical condition, history of epileptic seizures, history of other psychiatric, neurological disorders or substantial brain damage, and contraindication to magnetic fields (metal objects, claustrophobia) according to established safety criteria. The study was approved by the regional biomedical research ethics committee (CPP IDF 7; protocol 04-38) and written informed consents were obtained from participants after complete description of the procedures.

*Neuroimaging:* T1-weighted structural MRI scan (3D FT-SPGR acquisition, TR=12.5 ms, TE=2.2 ms, 124 slices, 256x256 view matrix, voxel size=0.9375x0.9375x1.3 mm) was carried out using a 1.5 Tesla whole-body system (Signa, GE, Milwaukee, WI, USA). PET imaging was performed on a Siemens ECAT HRRT 3D-PET scanner (CTI, Knoxville, TN, USA) with [<sup>11</sup>C]PE2I radiotracer, as previously described (Artiges et al., 2017; Dubol et al., 2018). Briefly, after a 6-minutes brain transmission scan performed using a <sup>137</sup>Cs point source to correct for tissue attenuation, the emission scan started with the intravenous bolus injection of about 300 MBq of [<sup>11</sup>C]PE2I and lasted for 60 minutes. Twenty sequential frames ranging from 1 to 5 minutes in duration were acquired in list mode. Images were reconstructed using the statistical algorithm OP-OSEM (Ordinary Poisson–Ordered Subset Expectation Maximization, 10 iterations using 16 subsets) including Point Spread Function (PSF) modelling for spatial resolution improvement. The voxel size was 1.2x1.2x1.2 mm<sup>3</sup>. A thermoplastic head mask was molded to each subject's face to restrain head movements, and head motion corrections were carried out post-reconstruction using the BrainVISA/Anatomist software (<http://brainvisa.info>). Brain regions were determined by T1-MRI automatic parcellation and applied on dynamic co-registered PET images using PMOD (Version 3.4, PMOD Technologies

Ltd, Zurich, Switzerland). Parametric maps of the regional [<sup>11</sup>C]PE2I non-displaceable binding potential (BP<sub>ND</sub>) were generated by PMOD's pixel-wise tool using the time-activity curves of dorsal striatum as high specific binding and crus1 sub-region of the cerebellum as a reference tissue, based on Gunn's basis function method (Gunn et al., 1997), which is closely related to the simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996). The suitability of specific [<sup>11</sup>C]PE2I binding quantification using a compartmental approach and the cerebellum as reference tissue has been validated by previous works (Hirvonen et al., 2008; Seki et al., 2010).

For image processing and analysis, we used SPM8 software (Wellcome Department of Cognitive Neurology, London, UK), implemented on Matlab<sup>®</sup>. The BP<sub>ND</sub> maps were spatially normalized using an in-house developed ligand-specific [<sup>11</sup>C]PE2I template generated according to an MRI-aided procedure (Meyer et al., 1999). The normalized BP<sub>ND</sub> maps were smoothed using a 10 mm FWHM Gaussian filter. The voxel size was 2×2×2 mm<sup>3</sup>. In order to include only main dopaminergic regions with sufficient detectable DAT levels in PET statistical analyses, we used a mask of analysis defined as all voxels with a minimum value of PET signal that was 50% superior to the maximum value of the crus1 area (cerebellar reference region). It included basal ganglia, midbrain, insula, amygdala, thalamus, and parts of anterior cingulate gyrus, inferior frontal cortex and temporal cortex (hippocampus, parahippocampal and superior temporal gyrus).

We compared the BP<sub>ND</sub> maps between the two groups using an ANCOVA model with age, daily tobacco consumption and gender as confounding covariates. In addition, three multiple regression analyses were carried out on BP<sub>ND</sub> maps to explore the relationships between DAT availability and clinical scores of depression and anxiety measured by the MADRS, BDI and STAI. For all statistical analyses, a threshold of p<0.05 Family Wise Error (FWE)-corrected was used, both at the voxel (height threshold) and the cluster (extent threshold) levels, in order to reduce type I errors introduced by potential noise.

## Results

*Characteristics of participants* (Table 1). In each group, half of the participants were smokers. No significant difference was found between MDD patients and healthy controls for age, tobacco daily consumption, gender distribution and state-anxiety. However, trait-

anxiety rating was higher in patients compared to healthy controls, as shown by the difference in STAI-T scores. The patients' MADRS scores ranged from 10 to 33, reflecting mild to marked severity of depressive symptoms (Muller et al., 2003).

*PET imaging results.* Between-group comparisons (Table 2; Figure 1) revealed lower  $BP_{ND}$  regional levels in MDD patients compared to healthy controls, denoting lower DAT availability in the patients. Significant differences were found in the superior part of the midbrain (right,  $p_{FWE}=0.002$ ; left,  $p_{FWE}=0.006$ ) including the substantia nigra and the ventral tegmental area, and in parts of the right putamen nucleus ( $p_{FWE}=0.012$ ). No region displayed higher DAT availability in MDD patients as compared with the healthy controls. The multiple regression analyses did not reveal any correlation between DAT availability and the patients' clinical scores.

## Discussion

This is the first report examining the DAT regional availability with voxel-based analysis in striatal and extra-striatal DA regions in patients diagnosed for major depression disorder, using HRRT PET imaging. Despite the small sample size, we found significant reduction in DAT availability predominantly in the midbrain of MDD patients compared with healthy controls. However, DAT availability did not relate to depression and anxiety assessments in our sample.

The previous imaging studies that assessed the DAT in a context of depression led to inconsistent findings, reporting higher, lower, or no change in striatal DAT availability in patients (for review, (Camardese et al., 2014)). Using a voxel-wise approach that does not require a priori defined ROIs, we detected a decreased striatal DAT availability in patients, which was restricted to the dorsal part of the right putamen. This finding suggests that the use of large predefined ROIs based on anatomic subdivisions could partly explain the discrepant findings among the previous studies. Although the striatum is the richest region in DAT proteins, the transporter can also be detected *ex vivo* to a lesser extent in extra-striatal regions including midbrain, hippocampus, amygdala, insula and the thalamus (Biegon et al., 1992; Little et al., 1995; Marcusson and Eriksson, 1988; Tupala et al., 2006). The use of HRRT coupled with a voxel-based approach enabled the detection of a lower DAT availability in the superior part of the midbrain including ventral tegmental area and substantia nigra in

the present depressed patients. Remarkably, although obtained in a small sample, this result is statistically significant ( $p_{FWE} < 0.006$ ). Moreover, the localization of this difference is particularly relevant, as the midbrain contains the cell bodies of the DA neurons resulting in the mesolimbic and nigrostriatal DA pathways. Interestingly, post-mortem observations point to lower extra-striatal DAT levels in depressed patients but no change in striatal regions (Bowden et al., 1997; Klimek et al., 2002), supporting the hypothesis of a specifically impaired mesolimbic DA pathway. Our results are in line with this hypothesis, as they indicate a lower extra-striatal DAT availability in depression, with moderate alteration of striatal DAT. Nonetheless, we cannot draw any conclusion about the involvement of the specific DA pathways in our results, as the spatial resolution of the PET images do not enable the distinction between the ventral tegmental area and the substantia nigra.

While this paper was in review, a PET study using a highly specific DAT radiotracer, [<sup>11</sup>C]altropane, reported a decrease of DAT availability in the bilateral putamen and the ventral tegmental area in 25 untreated MDD patients (Pizzagalli et al., 2019). Despite differences in sample size and drug status of the patients, these results are remarkably comparable with our findings.

The DAT represents a useful functional marker of the dopaminergic system. It can undergo long-term regulations, as demonstrated by the decrease in DAT density following chronic DA depletion (Gordon et al., 1996). Consequently, a lower DAT availability in depressed patients should represent an adaptive functional change due to blunted DA function, resulting in lower membrane expression of the DAT protein. This interpretation is further supported by the numerous studies that point to a blunted DA transmission in depression, including reduced levels of DA metabolites (Lambert et al., 2000; McClure, 1973) and the significant impact of pharmacological DA manipulations on depressive symptoms (Bremner et al., 2003; Hasler et al., 2009; Leggio et al., 2013). Another possible interpretation of our results would be to consider a reduced DAT availability as a marker of lower DA neurons density or structural integrity. Indeed, as the DAT is specifically expressed on the surface of DA neurons, it constitutes an anatomical marker of the DA pathways (McHugh and Buckley, 2015). Thus, the lower DAT availability we observed in MDD patients could result from a blunted DA function, a structural alteration of DA neurons, or both. Further investigations will be needed to confirm this observation and determine the specifications of DA dysregulation in depression.



Some limitations of the study are acknowledged. The first is the smallness of the patient sample and the related limited statistical power that could account for the absence of relation between DAT availability and the clinical scores, implying caution in the interpretation of the findings. Second, and in line with this, the sample size did not allow us to investigate the impact of antidepressant treatments on DAT availability measures. Indeed, although most antidepressants (except sertraline and nomifencine) are not potent for the DAT (Tatsumi et al., 1997), we cannot exclude an indirect causal effect of antidepressant treatments on the findings. This is unlikely however, as SSRIs and tricyclic antidepressants induce an up-regulation of the DAT protein both in human and animal studies (Chen and Lawrence, 2003; Kugaya et al., 2003; Rominger et al., 2015), as opposed to our result. Moreover, an effect of antidepressants could not account for the specific localization of the present findings within the midbrain, as these compounds do not target the DAT in this region only. A third limitation arises from the lack of behavioral and clinical features assessing relevant dimensions of the depressive symptomatology that might relate to the DA function (such as motivational anhedonia measures).

In conclusion, although obtained in a small group of depressed participants, the present findings highlight alterations mainly located in core dopamine midbrain nuclei, where most of the dopamine is produced. The findings further support a lower presynaptic DA function in depressed patients, and suggest that investigations on the role of midbrain DA in the pathophysiology of depression are needed.

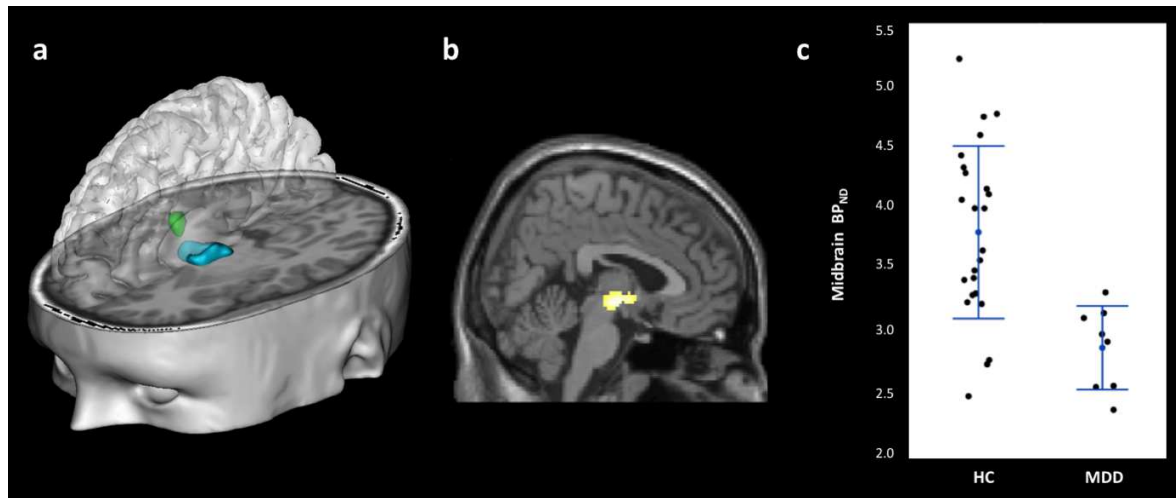
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Declarations of interest: None

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**Figure 1. Between-groups comparison: lower DAT availability in MDD patients as compared with healthy controls.** (a) Three-dimensional rendering of the healthy controls > patients clusters in the midbrain (in blue) and the right dorsal putamen (in green), obtained using BrainVisa software. (b) Sagittal slice view of the comparison HC > MDD T-map, showing the midbrain cluster ( $x=4$ ). (c) Scatterplot of mean raw BP<sub>ND</sub> values extracted from the midbrain cluster. Error bars indicate  $\pm 1$  standard deviation. HC, healthy controls; MDD, major depressive disorder patients; BP<sub>ND</sub>, non-displaceable Binding Potential.

## Tables

<i>Characteristic</i>	<i>MDD (n=8)</i>	<i>HC (n=24)</i>	<i>Group Comparison</i>	
			<i>T-value</i>	<i>p-value</i>
Age (years)	40.50 (11.45)	34.25 (9.62)	1.52	0.14
Gender (Male/Female)	6/2	21/3	-	0.42
Tobacco consumption (cig/day)	4.63 (10.45)	8.54 (10.16)	0.93	0.36
STAI-T	45.28 (7.08)	34.54 (9.98)	2.64	0.01
STAI-S	30.14 (6.67)	25.83 (6.98)	1.45	0.16
MADRS	22.0 (11.93)	-	-	-

**Table 1. Participants' characteristics.** Mean (SD). HC, healthy controls; MDD, major depressive disorder patients; STAI, State-Trait Anxiety Inventory; MADRS, Montgomery-Åsberg Depression Rating Scale. Group comparisons were carried out using Student T-tests for age, tobacco consumption and MADRS variables. A chi-square test (Fisher's Exact test) was used to compare the groups in terms of gender distribution.

Region	Cluster Level		Peak Level				
	Cluster Size (Voxels)	p FWE Corrected	Peak Voxel t Value	p FWE Corrected	MNI Coordinates		
					x	y	z
R Midbrain (VTA/SN)	369	0.0004	5.77	0.002	8	-2	-4
R Midbrain (VTA/SN)			5.67	0.003	4	-12	-6
L Midbrain (VTA/SN)			5.36	0.006	-4	-2	-4
R dorsal Putamen	69	0.011	5.05	0.012	24	-10	8

**Table 2. Between-groups comparison: regions where DAT availability was lower in MDD patients as compared with healthy controls.** L: left; R: right; MNI: Montreal Neurological Institute; SN: Substantia Nigra; VTA: Ventral Tegmental Area.