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Review

Imaging studies on dopamine transporter and depression: A review of literature and suggestions for future research

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ABSTRACT

We review the conflicting results from imaging studies of dopamine transporter availability in depressed patients and also discuss the heterogeneity of the variables involved. Major depression includes diverse clinical manifestations and in recent years there has been an increasing interest in the identification of homogeneous phenotypes and different clinical subtypes of depression, e.g. anhedonic depression, retarded depression, etc. In addition, the use of different radioligands and imaging techniques, diverse rating scales, together with the lack of control of clinical variables (clinical course, recent or past use of substances of abuse, etc.) make it difficult to clearly identify neuronal regions or networks with consistently abnormal structures or functions in major depressive disorder. It is probably necessary to build a shared approach between clinicians and researchers in order to identify standardized procedures to better understand the role of the dopamine transporter in depression. We outline a list of major issues and also suggest some standardized procedures in collecting clinical and imaging data on major depressed patients. Our aim is to delineate a possible "modus operandi" that would be a proposal for neuroreceptor studies on major depression.

1. Introduction

Depression significantly affects people worldwide. The World Mental Health Day on Oct 10, 2012 focused on depression as a global crisis (for more see http://www.wfmh.org/00WorldMentalHealthDay.htm) and depression is estimated to affect 350 million people as a leading cause of disability worldwide in terms of total years lost due to disability.

Although biochemical, pharmacological, chronobiological and brain imaging techniques have been used to shed light on the neurobiology of mood disorders, our knowledge of the underlying pathophysiology remains unclear, partly due to the non-homogeneous clinical features. Major depressive disorders (MDD) are clinically diverse, including multiple subgroups. They symptomatically overlap with other psychiatric syndromes and are further confounded by several comorbid conditions.

The assumption that clinical depression might result from a reduction in the efficiency of one or more brain synapse types, using monoamines, such as serotonin, dopamine or norepinephrine is known as the monoaminergic hypothesis (Schildkraut, 1965). Dopamine (DA) is a neurotransmitter which plays a crucial role in brain mood regulation and is also involved in reward and motivation circuits. Multiple sources of evidence support the hypothesis of a decreased dopaminergic neurotransmission in major depression. It has long been known that substances which increase dopamine levels, such as cocaine and amphetamine, lead to mood elevation; conversely, drugs which reduce dopamine levels (such as reserpine) or block dopamine receptors (such as neuroleptics) can induce either dysphoria or depressed mood (D'Aquila et al., 2000). Medications which increase dopamine levels in the brain by inhibiting dopamine reuptake (e.g. bupropion) or acting as dopaminergic agonists (e.g. pramipexole) have proven to be potent antidepressants (Lattanzi et al., 2002).

Early evidence from clinical investigations supports the finding that depressed patients (in particular those with anhedonia and retardation) have reduced cerebrospinal (CSF) levels of homovanillic acid (HVA), the major metabolite of dopamine in the central nervous system (Bowers et al., 1969). On the other hand, patients with a personal or family history of psychotic disorders and depression with strong delusional features, generally show higher CSF concentration of HVA (Lykouras et al., 1994). DA turnover, assessed post-mortem, is also reduced in the caudate nucleus and

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nucleus accumbens of depressed suicides (Bowden et al., 1997). As DA uptake is unchanged in depressed suicides, the decreased turnover apparently reflects decreased DA release. In agreement with these findings, a decrease in 24-h urinary excretion of HVA and 3,4-dihydroxyphenylacetic acid (DOPAC) has been reported in depressed suicide attempters (Roy et al., 1992). As abnormalities of DA metabolism are not observed in non-depressed subjects attempting suicide, these data provide further evidence that decreased DA turnover is correlated to depression.

The development of neuroimaging techniques has enabled the investigation of structural and functional abnormalities in living depressed patients. Unfortunately, the diverse imaging techniques employed, the relatively small and heterogeneous samples studied, and the limited consistency of results across imaging procedures make it difficult to clearly identify neuronal regions or networks with consistently abnormal structures or functions in MDD.

In recent years there has been a growing interest in the identification of homogeneous phenotypes of depression (Hasler et al., 2004), such as anhedonic depression (Pizzagalli et al., 2005) or retarded depression (Leventhal et al., 2008). The identification of these phenotypic "subtypes" based on specific symptomatic clusters may constitute the clinical condition of which to investigate the specific genetic, biological and neurophysiological backgrounds supporting them (Gottesman and Gould, 2003; Hasler et al., 2004). A dimensional framework of the psychopathology of depression allows the formulation of more accurate psychobiological models of the disorder and, in particular, the main components of the clinical picture. According to this approach, correlations were found among symptoms, such as cognitive deficits, rumination, psychomotor retardation, anhedonia or decreased mood and specific focal abnormalities of cerebral blood flow (Drevets, 2000; Mayberg et al., 1999).

The physiological alterations underlying reduced dopamine signalling could result from either diminished DA release from presynaptic neurons or from impaired signal transduction and thus from changes in receptor number or function and/or altered intracellular signal processing. Neuroimaging studies investigating the role of pre-and post-synaptic dopamine levels were conducted using various radioligands specifically binding to dopamine transporter (DAT), D_1 (dopamine 1) or D_2 (dopamine 2) receptors. Presynaptic DAT is among the most investigated targets, also due to the availability of radioligands commonly used in movement disorders (Di Giuda et al., 2012).

The aim of our review is to analyze the conflicting results of the main findings from imaging studies of DAT in depressed patients. Furthermore, a possible working approach for future neuroimaging research on DAT and depression is suggested.

2. Materials and methods

In order to thoroughly explore the relationship between DAT availability and depression, a PubMed search was conducted using the terms "depression", "dopamine transporter", "mood disorders", "PET", "SPECT" and "neuroimaging". We included all 15 original published reports in this review.

In the results section, below, we present an overview of the main findings according to the imaging technique and specifically to the radioligand employed (for details of each study see Table 1).

In the discussion section, we consider the possible reasons for the inconsistencies in the literature (where they exist), outlining the main limitations of the studies and also identifying a list of critical topics focussing on the recruited sample, the diagnostic categories, the clinical course variables, the rating procedure and different radiotracers. Finally, we formulate some hypotheses about the role of DAT in the pathophysiology of depression and also

Table 1
Neuroimaging human studies on dopamine transporter (DAT) availability and depression.

Study	Subjects N + mean age	Illness length	Rating scales	Diagnosis	Therapy	Ligand	Results	Major limitations
Malison et al., 1998a,b	Pts = 15 44 ± 10 Ctr = 15 45 ± 11	n/a	Yale Depression Inventory (YDI) ≥17	MDD 5 Pts: single-episode 10 Pts: recurrent depression Comorbidity: 4 Pts: (1) attention deficit disorder; (1) alcohol and marijuana dependence in remission; (1) dysthymia, primary type; (1) panic disorder with agoraphobia in remission According to DSM-III-R	Drug free ≥ 3 weeks Antidepressant free: 81 ± 134 weeks 6/15 Pts: drug naive	[^{123}I]-β-CIT	= Striatal V''_3 values (DAT) between patients and controls. − Brainstem V''_3 values (SERT) in patients vs. controls. No correlation between ^{123}I-β-CIT uptake (striatal and brainstem V''_3) and behaviour-related outcome measures (YDI, HAM-A, BDI and CGI).	- Small sample size; - Heterogeneity of diagnosis; - Effect of previous psychotropic medications exposure; - Daily alcohol consumption and smoking habits were not controlled.
Laasonen-Balk et al., 1999	Pts = 15 36.1 ± 8.1 Ctr = 18 35.2 ± 5.9	n/a	HAMD-17 16.3 ± 7.4 MADRS 21 ± 5.8	MDD According to DSM-III-R	Drug naive	[^{123}I]-β-CIT	+ DAT density (striatum-to-white matter ratio) in patients vs. controls. No significant correlations between severity of depression (MADRS, HAMD and BDI) and DAT density. No significant correlations between	- Relatively small sample size; - Use of the white matter instead of the cerebellum as region of interest; - Daily alcohol consumption and smoking habits were not controlled.

							the psychomotor retardation score item n° 8 in the HAMD and DAT density.	
Meyer et al., 2001	Pts = 9 35 ± 8 Ctr = 23 37 ± 10	n/a	HAMD-17 21 ± 3.8	MDD According to DSM-IV	Drug free ≥ 3 months 5/9 Pts: drug naïve	[^{11}C]RTI-32 PET	− DAT BP in patients vs. controls in bilateral caudate and putamen. Significant inverse correlation between striatal DAT BP and neuropsychological tests (Pts with lower DAT BP performed better on the Finger Tapping Test and the Stroop Colour-Word Test).	- Small sample size; Effects of previous medication exposure; possible differences in illness length and episode duration; daily alcohol consumption was not controlled.
Neumeister et al., 2001	Pts = 11 30.5 ± 8.4 Ctr = 11 31.3 ± 9.8	n/a	SIGH−SAD 32.7 ± 5.1	SAD (Rosenthal criteria, '84) MDD According to DSM-IV	Drug free	[^{123}I]-β-CIT	− V''_3 values DAT in patients vs. controls in the left striatum. No correlation between SIGH−SAD total score and V''_3 DAT	- Very little sample size; unbalanced sample according to the gender; - Heterogeneity of diagnosis; - Effect of previous medications exposure (authors did not report if patients were drug naïve and/or only the medication-free interval).
Brunswick et al., 2003	Pts = 15 40 ± 12 Ctr = 46 40 ± 11	n/a	HAMD-17 22 ± 4	10 MDD 5 BP II According to DSM-IV	No antidepressants ≥7 days No MAOIs ≥2 weeks No fluoxetine ≥3 weeks	[^{99m}Tc]TRODAT-1	+ [^{99m}Tc] TRODAT-1 binding in the right anterior putamen (23%), right posterior putamen (36%), left posterior putamen (18%) and left caudate nucleus (12%) in patients vs. controls.	- Relatively small sample size; - Diagnostic heterogeneity; - Differences in illness length and episode duration; - Smoking habits were not controlled.
Argyelan et al., 2005	Pts = 16 39 ± 13 Ctr = 12 34 ± 14	n/a	HAMD-21 Baseline 26.67 ± 5.77 Week 4 ($N = 9$) 16.10 ± 6.42	MDD According to DSM-IV	Drug free ≥ 6 months 7/16 Pts: drug naïve 9 Pts take bupropion for 4 weeks	[^{99m}Tc]TRODAT-1	= DAT SOR at baseline between groups. Correlation between baseline SOR and HAMD score change.	- Relatively sample size; differences in illness length and episode duration; - Lack of drug monitoring; - Smoking habits were not controlled.
Lehto et al., 2006	Pts = 29 MI: 28.10 ± 8.1 Und: 32.3 ± 11.4 Atd: 25.4 ± 5.8 Ctr = 18 30.5 ± 9.18	n/a	HAMD-21 MI: 26.8 ± 6.5 Und: 19.1 ± 3.4 Atd: 18.3 ± 4.5 HAMD-29 MI: 32.8 ± 8.8 Und: 27.2 ± 5.5 Atd: 28.6 ± 9.6	MDD According to DSM-IV-TR 10 Melancholics pts (MI) 8 Undifferentiated pts (Und) 11 Atypicals pts (Atd)	Drug naïve	[^{123}I]nor-β-CIT	= DAT density between subgroups of depressed patients and vs. controls. No association between striatum DAT densities and symptoms or the subtype of depression.	- Relatively small sample size; - Heterogeneity of patient populations; - Differences in illness length and episode duration; - Daily alcohol consumption and smoking habits were not controlled.
		n/a				[^{123}I]-FP-CIT		

(*continued on next page*)

Table 1 (*continued*)

Study	Subjects N + mean age	Illness length	Rating scales	Diagnosis	Therapy	Ligand	Results	Major limitations
Sarchiapone et al., 2006	Pts = 11 41.1 ± 11.9 Ctr = 9 35.6 ± 11.3		HDRS 20.4 ± 6.3 MADRS 21.6 ± 2.4	9 MDD (3 with double depression DD) 2 BP II All pt was anhedonic (SHAPS: 9.5 ± 1.8) According to DSM-IV-TR	Drug free ≥ 4 weeks 6/11 Pts: drug naïve		− DAT binding in patients vs. controls in the striatum. No correlation between DAT binding ratios and scores on SHAPS, HDRS, HARS and MADRS.	- Little sample size; heterogeneity of the patient populations; - Effect of previous medication exposure; - Daily alcohol consumption and smoking habits were not controlled.
Newberg et al., 2007a,b	58 No depressed subjects 35 ± 12 POMS < 3 35.5 POMS > 3 34.8	n/a	n/a	POMS < 3 N = 45 POMS > 3 N = 13	Drug free	[^{99m}Tc]TRODAT-1	+[^{99m}Tc]TRODAT-1 DVRs in the right caudate of subjects with POMS > 3 vs. subjects with POMS < 3. Correlation between higher [^{99m}Tc]TRODAT-1 DVRs in the right caudate and depressive symptoms scores.	- Relatively modest sample size; - Imbalance among the subjects in the two groups; - Smoking habits were not controlled.
Yang et al., 2008a,b	Pts = 10 50.5 ± 7.2 Ctr = 10 52.8 ± 6.3	3.4 ± 7.1 weeks	HAMD-17 25.2 ± 7.6	MDD According to DSM-IV	Drug free ≥ 3 months After baseline SPECT, Pts were prescribed antidepressants for 4 weeks	[^{99m}Tc]TRODAT-1	+[^{99m}Tc]TRODAT-1 St/Oc ratio in patients vs. controls. Pre-treatment DAT availability correlated marginally with HAMD improvement after 4 weeks treatment.	- Small sample size; - Current smoking status; - Authors did not report any control about the use of substance of abuse.
Lehto et al., 2008	Pts = 19 MD = 11 31.3 ± 5.9 DD = 8 23.4 ± 4.6 Ctr = 19 30.6 ± 8.9	Duration MD (months) MD = 26.7 ± 47.3 DD = 11.8 ± 12.4 Duration DD DD = 66 ± 35.14	HAMD-17 MD = 20.9 ± 6.3 DD = 16 ± 3.21	MDD MD = 11 DD = 8 According to DSM-IV	Drug naïve After baseline SPECT, patients underwent 1 year of psychodynamic psychotherapy	[^{123}I]nor-β-CIT	= [^{123}I]nor-β-CIT binding between depressed groups and controls. No difference between DD and MD groups in striatum binding of [^{123}I]nor-β-CIT. − Striatum [^{123}I]nor-β-CIT binding in DD with longer episode duration.	- Relatively small sample size; - Heterogeneity of patient populations; - Current smoking status of some patients.
Hsieh et al., 2010	Pts = 13 (euthymic with a history of MDD) 40.62 ± 8.65 Ctr = 26 40.92 ± 9.47	History of major depression (years) 9.12 ± 8.57	HAMD-17 ≤7 Mean 4.15 ± 1.68	Euthymic patients	Drug free ≥ 3 months Mean (months) 31.92 ± 26.57	[^{123}I]ADAM for SERT [^{99m}Tc]TRODAT-1 for DAT	= DVRs of SERT or DAT between healthy subjects and euthymic patients with a history of major depression. No difference in laterality for DRV of DAT was found between the study groups. Author's comment: therefore SERT and DAT DVRs may not be trait markers for patient with major depression.	- Relatively small sample size; - Effect of previous antidepressant therapy on transporters levels.
Wu et al., 2011					Drug free ≥ 2 years	[^{99m}Tc]TRODAT-1		

	PD Pts = 17 55 ± 12 MDD Pts = 13 51 ± 11 Ctr = 10 47 ± 13	Duration of disease (months) PD = 14 ± 6 MDD = 7 ± 3	HAMD-17 PD < 14 MDD > 24	PD = 17 ICD-10 MDD (plus psychomotor retardation) = 13 According to DSM-IV			– [^{99m}Tc]TRODAT-1 right striatum/ cerebellum and left striatum/cerebellum ratios in MDD and PD vs. healthy subjects. Decrease more dramatically in PD than MDD.	- Small sample size; - Clinical psychomotor retardation was not rated by any instrument; - Smoking habits were not controlled.
Amsterdam et al., 2012	Pts = 39 41.4 ± 11.8 Ctr = 84 37.5 ± 14.5	Mean illness length (years) 24 ± 10.9 Mean current depressive episode duration (months) 19.4 ± 20.9	HAMD-17 ≥16	MDD = 24 BP II = 15 According to DSM-IV-TR	Drug free ≥ 6 months 21/39 Pts had prior exposure to a mean 3.1 ± 2.4 psychotropic medications. 18/39 Pts had never taken psychotropic medications	[^{99m}Tc]TRODAT-1	+ DAT DVR values in the putamen and the combined putamen plus caudate regions in patients vs. controls. = DAT DVR values between unipolar and bipolar depressed subjects. = DAT DVR values for depressed subjects with or without prior Ads exposure. Significant predictive probability of the putamen or putamen plus caudate DVR value to distinguish depressed from non-depressed subjects.	- Relatively small sample size; - Heterogeneity of diagnosis; - Broad age range of study participants; - Differences in illness length and episode duration; - Prior antidepressant exposure; - Lack of drug monitoring.
Hsiao et al., 2013	Pts = 23 36.2 ± 10.1 Ctr = 20 38.3 ± 14.9	n/a	HAMD-17 Women Remitted: 23.2 ± 5.5 No remitted: 26.0 ± 4.1 Men Remitted: 25.1 ± 3.9 No remitted: 21.3 ± 7.4	MDD = 23 According to DSM-IV-TR	Drug free ≥ 6 months 8-weeks bupropion treatment: 150 mg/day × 3 days then 300 mg/day to the end	[^{99m}Tc]TRODAT-1	+ Baseline mean specific uptake ratio (SUR30) values in depressed patients than controls on both sides of striatum. DAT binding was significantly reduced after 8 weeks of bupropion treatment. Pts with initially higher DAT levels showed greater decreases in DAT after bupropion treatment No correlation between the effectiveness (HAM-D score changes) and DAT binding. Depressed women but not healthy women have more DAT availability	- Relatively small sample size; - Lack of drug monitoring.

Abbreviations: + (*higher*); – (*lower*); = (*no difference*); Pts (*patients*); CTR (*controls*); N/A (*not available*); MDD (*major depressive disorder*); BP II (*bipolar type 2 disorder*); DD (*double depression*); SAD (*seasonal affective disorder/ winter type*); PD (*Parkinson's disease*); SPECT (*single-photon emission computed tomography*); HDRS (*Hamilton Depression Rating Scale*); HAM-D (*Hamilton Depression Rating Scale*); HAM-A (*Hamilton Anxiety Rating Scale*); BDI (*Beck Depression Inventory*); MADRS (*Montgomery–Åsberg Depression Rating Scale*); SHAPS (*Snaith–Hamilton Pleasure Scale*); CGI (*Clinical Global Improvement Scale*); POMS (*Profile of Mood States*); SIGH–SAD (*Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version*); DAT (*dopamine transporter*); SERT (*serotonin transporter*); Ads (*antidepressants*); MAOIs (*monoamine oxidase inhibitors*); BP (*binding potential*); V''_3 (*specific-to-non displaceable equilibrium partition coefficient*); SOR (*specific/non-specific activity ratio*); SUR30 (*specific uptake ratio corrected for age*); DVRs (distribution volume ratios); St/Oc ratio (*striatum/occipital ratio*); ^{123}I-β-CIT (*[^{123}I]β-carbomethoxy-3β-(4-iodophenyl)tropane*); [^{11}C]RTI-32 PET (*^{11}C-methyl (1R-2-exo-3-exo)-8-methyl-3-(4-methylphenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate*); [^{99m}Tc]TRODAT-1 (*[^{99m}Tc][2[[2-[[[3-(4-chlorophenyl)-8-methyl-8a2abicyclo[3.2.1]oct-2-yl]-methyl](2-mercaptoethyl)amino]ethyl]amino]ethance-thiolato(3-)-N2,N2′,S2,S2′]oxo-[IR-(exo-exo)]*); [^{123}I]nor-β-CIT (*[^{123}I]-nor-2-β-carbometoxy-3-β-(4-iodophenyl)-tropane*); ^{123}I-FP-CIT (*^{123}I-N-ω–fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane*); [^{123}I]ADAM (*[^{123}I] 2-((2-((dimethylamino)methyl)phenyl)thio)-5-iodophenylamine*); vs. (*versus*).

suggest some standardized procedures in collecting clinical and imaging data on major depressed patients.

2.1. Studies with [^{99m}Tc]TRODAT-1

The literature search yielded eight studies using [^{99m}Tc]TRODAT-1 as radioligand for SPECT imaging [^{99m}Tc]TRODAT-1 is the most specific radioligand for DAT (Dresel et al., 1998). The majority of studies have detected a greater availability of dopamine transporter in depressed patients with MDD. The first investigation was performed by Brunswick et al. (2003) who found that DAT levels were higher in areas of the basal ganglia in 15 depressed patients with respect to healthy subjects (Brunswick et al., 2003). Examining 58 healthy subjects with and without depressive affects, Newberg et al. (2007a,b) found that healthy subjects with high Profile of Mood States scores (POMS score >3) showed significantly greater age corrected [^{99m}Tc]TRODAT-1 distribution volume ratio (DVR) in the right caudate compared to healthy subjects with POMS score <3 (Newberg et al., 2007a). More recently, significantly greater DVR values in the putamen and caudate of depressed patients versus healthy controls have been also reported by Amsterdam et al. (2012). This relevant study has investigated 39 patients with a current depressive episode among whom 24 met the DSM-IV-TR criteria for unipolar major depressive disorder (MDD) and 15 for bipolar type II disorder. All patients were drug free within the previous 6 months and 18 subjects were drug naïve. Of note, they did not find any significant difference in DVR values between unipolar and bipolar depressed patients as well as in patients with or without prior antidepressant treatment. According to their findings, the authors suggested that greater DVR values of striatal DAT measured by [^{99m}Tc]TRODAT-1 may be a potential diagnostic biomarker of a depression state.

On the contrary, in a dual-isotope SPECT study assessing serotonin transporter (SERT) and DAT levels by means of [^{123}I]ADAM and [^{99m}Tc]TRODAT-1, respectively, Hsieh et al. failed to identify significant differences in the DVRs between patients with a history of major depression in euthymic state (HAM-D <7) and healthy controls. The authors speculated that DVRs of SERT and DAT may not be trait markers for major depression (Hsieh et al., 2010).

The only [^{99m}Tc]TRODAT-1 study reporting a significantly lower DAT availability in depressed patients was performed by Wu et al. The authors assessed a clinical population of 13 severely depressed patients with psychomotor retardation, 17 subjects with Parkinson's disease and 10 healthy controls. They found that [^{99m}Tc]TRODAT-1 radio signal was significantly lower both in depressed patients and subjects with Parkinson's disease, although the reduction was more severe in subjects with Parkinson's disease (Wu et al., 2011). However, the results obtained in depressed subjects should be interpreted with caution because the researchers compared very small groups of patients and they did not rate psychomotor retardation.

Concerning [^{99m}Tc]TRODAT-1 studies before and after antidepressant treatment, Argyelan et al. assessed DAT availability in 16 depressed patients and 12 healthy subjects. All patients were drug free for at least 6 months and 7 patients were drug naïve. After baseline SPECT examination, bupropion was administered to 9 of the 16 depressed patients and a second SPECT scan was carried out after 4 weeks of treatment. Although no differences in baseline DAT striatum–occipital ratio (SOR) between depressed patients and healthy subjects were detected, the 9 treated patients showed a significant increase in the baseline SOR values after 4 weeks of bupropion treatment. The authors did not find any correlation between the efficacy of therapy and DAT occupancy (Argyelan et al., 2005).

More recently, Yang et al. performed a dual-isotope SPECT study in 10 drug-free depressed subjects and 10 healthy controls, using simultaneously [^{123}I]IBZM for D_2/D_3 receptors and [^{99m}Tc]TRODAT-1 for DAT. Depressed patients showed significantly higher DAT binding in comparison with healthy subjects; however, there were no significant differences in D_2/D_3 receptor availability. After 4 weeks of antidepressant treatment (fluoxetine, paroxetine and venlafaxine), baseline striatal DAT availability correlated marginally with HAM-D improvement, whereas no correlations were observed for D_2/D_3 receptor availability (Yang et al., 2008b). This result was in contrast with the previous findings of Argyelan et al. (2005), who reported a negative correlation between DAT availability and changes in HAM-D scores after bupropion treatment.

Lastly, Hsiao et al. assessed DAT availability in depressed patients before and after bupropion treatment. They reported that the baseline mean specific uptake ratio (SUR) values were significantly higher in 23 drug-free depressed patients compared to 20 healthy controls on both sides of the striatum. Interestingly, DAT binding was significantly reduced after 8 weeks of bupropion treatment. In agreement with Argyelan et al. (2005), the authors also reported that patients with initially higher DAT levels showed greater decreases in DAT after bupropion treatment, although there was no correlation between the clinical outcome (HAM-D score changes) and DAT binding. They postulated that the main role of DAT in depression is to mediate treatment resistance, as opposed to treatment response (Hsiao et al., 2013).

In conclusion, although a greater DAT availability has been more frequently reported in depressed patients using [^{99m}Tc]TRODAT-1 SPECT, a clear interpretation of overall results cannot be discussed. In fact, [^{99m}Tc]TRODAT-1 investigations present many limitations as well as some confounders that we have commonly found in the majority of DAT imaging studies. In particular, the sample sizes were relatively modest and several factors such as substance abuse, smoking habits or medication status were not controlled. Moreover, the clinical population was not very homogeneous according to the diagnosis and data were also obtained in patients suffering from different clinical conditions other than MDD (bipolar patients or euthymic subjects) (Amsterdam et al., 2012; Brunswick et al., 2003; Newberg et al., 2007a). However, starting from the considerations of Amsterdam et al. and Hsieh et al. (Amsterdam et al., 2012; Hsieh et al., 2010), we also assume that a greater DVR of DAT measured with [^{99m}Tc]TRODAT-1 could be a potential state marker of a depressive episode. In fact, these two studies have clearly demonstrated a greater DAT availability only in subjects examined during a depressive episode (both unipolar and bipolar patients), but not in an euthymic state. Concerning pharmacotherapy, DAT could represent a treatment resistance marker because the higher the basal level of DAT binding, the larger the decrease after treatment although not necessarily related to depressive symptom changes (Hsiao et al., 2013).

Overall, because of its specificity for DAT, [^{99m}Tc]TRODAT-1 seems to be a suitable SPECT radiotracer for future imaging studies of DAT availability in major depression.

2.2. Studies with ^{123}I-β-CIT

Three SPECT studies examined DAT availability using ^{123}I-β-CIT as radioligand. ^{123}I-β-CIT is not specific for DAT binding, showing high affinity for both serotonin (Laruelle et al., 1993) and norepinephrine transporters (Farde et al., 1994). The results of these studies are conflicting as one of them did not find significant differences, one a greater availability and the other a lower availability of DAT in subjects with depressive symptomatology versus healthy controls. In particular, Malison et al., who performed one of the first SPECT studies in depressed patients, did not find differences in striatal V''_3 values (ratio of specific to nonspecific brain uptake) in comparison with healthy subjects. However, a significant lower

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brainstem V''_3 value (a measure of SERT availability) was detected (Malison et al., 1998a). Laasonen-Balk et al. obtained interesting results in 15 drug-naïve depressed patients (DSM-III-R). They found a significantly higher ^{123}I-β-CIT uptake (striatum-to-white matter ratio) in depressed patients than in 18 healthy controls. On the other hand, no significant correlations between the severity of depression and DAT density were observed (Laasonen-Balk et al., 1999). The third intriguing study was carried out by Neumeister et al. in 11 drug-free depressed patients (DSM-IV) who also met Rosenthal criteria for seasonal affective disorder/winter type SAD. The authors reported significantly lower V''_3 values (specific-to-non-displaceable partition coefficient) in the left striatum of depressed patients in comparison with controls (Neumeister et al., 2001).

The findings obtained using ^{123}I-β-CIT needs some caveats. Firstly, as mentioned above, ^{123}I-β-CIT is not a specific radioligand for DAT due to its affinity also for norepinephrine and serotonin transporters. Unfortunately, only Malison et al. reported concomitant data about SERT availability and it is not possible to role out that a reduced or increased serotonin or norepinephrine transporter availability may alter DAT results in all the three studies. Secondly, the discrepancy between these data may come from differences in the groups of patients examined. Neumeister et al. studied an unbalanced gender sample of depressed patients with high rates of retardation, whereas Malison et al. subjects with high levels of comorbidity. Thirdly, the results of Laasonen-Balk et al. are not comparable with those of the above mentioned studies because the authors used the white matter rather than the cerebellum as reference region. Overall, in our opinion ^{123}I-β-CIT is not a suitable radiotracer for research in major depression due to its scarce specificity for DAT .

2.3. Studies with [^{123}I]nor-β-CIT

The literature search yielded two SPECT studies using [^{123}I]nor-β-CIT as radioligand. Carried out by the same group, these investigations reported no significant differences in striatal DAT densities of depressed patients versus controls. It is worth noting that [^{123}I]nor-β-CIT is not specific for DAT binding; in fact, this radioligand binds to the noradrenergic transporters (NORT) and, in addition, is considered to be more serotonin-specific (Hiltunen et al., 1998). The first study was aimed to assess mainly the midbrain SERT density in subgroups of depressed patients versus healthy subjects. The authors did not find significant differences in either SERT or DAT densities between the depressed subgroups and controls (Lehto et al., 2006). Conversely, the second study was specifically aimed to explore the role of DAT and SERT in double depressed patients (major depression plus dysthymia). Patients also underwent 1 year of psychodynamic psychotherapy immediately after inclusion in the study. Although the dysthymia and major depression groups did not differ in age-adjusted baseline striatum or midbrain [^{123}I]nor-β-CIT binding or its change during psychotherapy, both patient groups showed lower midbrain [^{123}I] nor-β-CIT binding levels than controls, whereas no differences were observed for striatum DAT binding levels. Interestingly, the authors found a lower striatum [^{123}I]nor-β-CIT binding in patients suffering from double depression with longer episode duration and they hypothesized that this may indicate temporal secondary adjustment of striatal DAT levels secondary to low dopamine levels (Lehto et al., 2008).

Owing the fact that [^{123}I]nor-β-CIT is a more serotonin-specific radioligand, we think that, as for ^{123}I-β-CIT, it is not a suitable tracer for future imaging studies on DAT availability in depressed patients. The [^{123}I]nor-β-CIT radioligand has also been reported to bind to striatal SERTs and thus the striatal uptake is a combination of DAT and SERT binding (Bergstrom et al., 1997).

2.4. Studies with ^{123}I-FP-CIT

^{123}I-FP-CIT is a commercially available dopamine transporter marker (DaTSCAN) for routine clinical use. This radioligand, which shows a high, although less selective affinity for DAT with respect to [^{99m}Tc]TRODAT-1, is widely used in movement disorders (Bajaj et al., 2013; Di Giuda et al., 2012). While the affinities of ^{123}I-β-CIT for DAT and SERT are equivalent and characterized by slow kinetics, ^{123}I-FP-CIT has the advantage of a higher selectivity for DAT and faster kinetics (Piccini, 2003).

Only one SPECT study used ^{123}I-FP-CIT as radioligand. This interesting investigation aimed to assess the striatal DAT density of depressed patients in whom anhedonia was a predominant feature. The authors evaluated 11 depressed patients with marked anhedonia (as measured by Snaith–Hamilton Pleasure Scale, SHAPS). All depressed patients had a SHAPS score > 7 and were drug-free within the previous four weeks (6 patients were drug naïve). In comparison with 9 healthy controls, anhedonic depressed patients showed significantly lower specific/non-specific DAT binding ratios in striatal regions. The authors hypothesized a down-regulation of DAT secondary to lower dopamine concentrations in the synaptic cleft (Sarchiapone et al., 2006). However, the results of this study should be interpreted very cautiously because of the small sample size and the clinical heterogeneity of depressed patients (unipolar, bipolar and comorbid dysthymic disorder).

Overall, we think that ^{123}I-FP-CIT may be a useful tool to investigate DAT availability in depression owing to its wide clinical use, even though its affinity for SERT may affect SPECT results.

2.5. Studies with [^{11}C]RTI-32

Although [^{11}C]RTI-32 is a PET tracer that specifically explores the density of DAT (Guttman et al., 1997), it also has nanomolar affinity for the noradrenaline transporter (NAT), whereas it shows a low affinity for the SERT (Carroll et al., 1995). Therefore, part of the decrease of [^{11}C]RTI-32 binding observed in depressed patients could be related to the loss of noradrenergic terminals. However, in our opinion, [^{11}C]RTI-32 may be considered a useful radiotracer for DAT assessment in depression. The literature search yielded only one study of DAT function in depressed patients using [^{11}C]RTI-32 as radioligand. In this PET study, a significantly lower striatal DAT binding potential (BP) was detected in the bilateral striatum of 9 depressed patients (according to DSM-IV-TR criteria) as compared with 23 healthy subjects (Meyer et al., 2001).

From a methodological point of view, it is worthy of mention the PET study performed by Martinot et al., who evaluated the pre-synaptic dopaminergic activity and its relationship with a specific psychopathological dimension, such as psychomotor retardation (Martinot et al., 2001). The authors used [18F] DOPA, a radiotracer that reflects the activity of the decarboxylating enzyme and the storage capacity of dopamine, but they did not investigate the DAT availability. For this reason, this study was not included in our review as well as in Table 1.

3. Discussion

Based on scientific literature, it is not possible to draw a definite conclusion on DAT availability in depressed patients. Conflicting results have been obtained, probably due to the heterogeneity of the variables involved which we aim to clarify and discuss.

The main difficulties in the interpretation of these findings are related to the scarce homogeneity of recruited samples concerning

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the clinical diagnosis as well as the diagnostic heterogeneity of major depression itself, according to the DSM criteria.

In most studies, DAT availability has been assessed in patients with MDD during a major depressive episode (MDE), consistent with the DSM-IV criteria. Nevertheless, in some cases the evidence came from patients during the euthymic phase (Hsieh et al., 2010) or from patients with a seasonal pattern (Neumeister et al., 2001) or, lastly, from patients with MDD according to the DSM-III criteria (Laasonen-Balk et al., 1999; Malison et al., 1998b).

Moreover, while some authors evaluated patients with a particular clinical profile according to specific psychopathological dimensions (such as marked anhedonia) (Sarchiapone et al., 2006), other authors investigated patients with specific clinical features, according to the DSM criteria (such as melancholic, undifferentiated or atypical features) (Lehto et al., 2006). Clinical course variables, such as the time since diagnosis, the episode duration, the lifetime number of episodes, etc. are frequently neglected and some authors also reported data about patients suffering from different conditions other than MDD. In particular, patients diagnosed with bipolar type II disorder (Amsterdam et al., 2012; Brunswick et al., 2003; Sarchiapone et al., 2006), dysthymia (Lehto et al., 2008) or depressed patients with comorbidity (dysthymia, anxiety disorder, attention deficit disorder and substance abuse) (Malison et al., 1998b; Sarchiapone et al., 2006) have been recruited in various studies. Lastly, in one case the evidence came from euthymic subjects (Newberg et al., 2007a).

In addition to the diagnostic heterogeneity, the use of different radioligands or neuroimaging techniques (SPECT versus PET) is a further major limitation in interpreting discrepancies. Although in this review we pooled studies based on the employed radioligand, we were hindered in reporting comparable results also with the same radiotracer.

When considering studies using the same radiotracer, we observed some trends (see Table 1). For instance, in the case of ^{99m}Tc-TRODAT-1, a greater availability of DAT has more frequently been reported in depressed patients. Conversely, for ^{123}I-FP-CIT, a lower DAT availability has been detected during an MDE as well as an inverse correlation between depressive symptoms and DAT levels in patients with Parkinson's Disease. A similar discrepancy has also been observed in the studies enrolling bipolar type II patients, which have been performed using the two different radioligands: [^{99m}Tc]TRODAT-1 (Amsterdam et al., 2012; Brunswick et al., 2003) and ^{123}I-FP-CIT (Sarchiapone et al., 2006).

Undoubtedly, both the heterogeneity of patient samples (according to the clinical diagnosis) and the different methodological approaches contribute to yielding conflicting results. Concerning semi-quantification methods, different procedures have been employed in the assessment of DAT specific binding ratio: simple manual drawing and manual positioning of bi-dimensional (2D) region of interest (ROIs) with or without the help of Magnetic Resonance (MR) imaging data, semi-automated and automated positioning of 2D ROIs and three-dimensional (3D) VOIs, voxel-based statistical analysis. Although many of these procedures have been tested and validated in several settings, the strengths and weaknesses of each approach have not yet been clearly established. On the other hand, important factors that should be taken into account are the dependence of SPECT quantification results on the specific gamma camera and associated equipment as well as the size of reference database (Badiavas et al., 2011; Djang et al., 2012; Tatsch and Poepperl, 2012).

Moreover, two other relevant issues in the field of depression neuroimaging research are pharmacological treatment and substance abuse. Even though a preliminary observation failed to report significant changes in DAT binding after serotonergic drug (citalopram) administration (Pirker et al., 1995), more recent data have demonstrated that antidepressants can alter DAT availability. In particular, the general assumption is that selective serotonin reuptake inhibitors (SSRIs) may increase striatal DAT density by reducing SERT availability. The mechanisms involved are still unknown, even if a modulation of the dopamine system by SSRIs was reported (Ichikawa and Meltzer, 1995). Kugaya et al. speculated that low extracellular dopamine induced by SSRIs is mainly due to the increase of DAT rather than the SSRI desensitization of the serotonin receptors located on dopamine terminals or on interneurons facilitating dopamine release (Kugaya et al., 2003). In line with the reports on SSRIs, Shang et al. demonstrated that venlafaxine (a serotonergic and noradrenergic antidepressant) mildly increased [^{123}I]beta-CIT binding to DAT in the striatum (Shang et al., 2007). On the other hand, a reduction of DAT availability has been observed in patients after a 4-week treatment with bupropion, a dopaminergic and noradrenergic antidepressant (NDRI) that has been thought to bind to DAT (Argyelan et al., 2005).

In light of this, it is noteworthy that the majority of studies did not rule out patients with a history of psychotropic drug use at all. Although, in many cases, no information has been reported on these drugs, any influence on DAT availability cannot be excluded, in an unpredictable way. Indeed, also by pooling data both from drug-naïve and drug-free patients, it is not possible to reach consistent results (see Table 1). A higher or equal or lower DAT availability has been found when considering drug-free subjects with a previous history of antidepressant therapy. On the other hand, in the three studies focused on drug-naïve subjects compared to healthy controls, an increase has been observed in the first (Laasonen-Balk et al., 1999) but no differences in the last two (Lehto et al., 2006, 2008). Once again, this problem has to be added to the previously discussed diagnostic and methodological heterogeneities.

Furthermore, current and/or past substance abuse represents another remarkable issue, often underestimated or not taken into account at all. For instance, very complex relationships link the use of alcohol to DAT availability and conflicting data have been reported. Lower DAT density was found in abstinent, non-violent alcoholics with respect to controls, whereas higher DAT density was reported in violent alcoholics (Tiihonen et al., 1995). Conversely, Volkow et al. found unchanged DAT availability in abstinent alcoholics as compared with controls (Volkow et al., 1996). On the other hand, Laine et al. described an initial reduction in DAT availability during the acute phase of alcohol withdrawal, followed by an increase of DAT over time, achieving control levels (Laine et al., 1999). More recently, it has been emphasized that discrepancies can be explained by the concomitant use of other psychotropic substances, such as nicotine. In line with this view, Cosgrove et al. reported differences in DAT availability between alcohol drinking smokers and non-smokers. The authors hypothesized that smoking may suppress the alcohol-induced increase in DAT availability during acute alcohol withdrawal (Cosgrove et al., 2009). These observations are also in agreement with the reported lower DAT availability in smokers versus non-smokers (Newberg et al., 2007b; Yang et al., 2008a). However, discrepancies related to smoking status have never been analyzed in depressed patients.

When considering the most frequently abused drugs, in addition to alcohol and nicotine, it is known that different substances can cause lasting changes of DAT that are not yet definitely clarified, nor considered in imaging studies on depression.

Methamphetamine (METH) has extensively been found to reduce DAT availability, even months to years after cessation, thus suggesting a specific neurotoxicity on dopamine terminals (Johanson et al., 2006; McCann et al., 1998; Sekine et al., 2001, 2003; Volkow et al., 2001). No data are available concerning DAT

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changes during cocaine abuse, even though a greater DAT availability has been described in abstinent cocaine-abusing subjects in comparison to healthy controls (Jacobsen et al., 2000; Malison et al., 1998a). In addition, Crits-Christoph et al. used a regression equation and estimated that DAT availability would return to normal levels by approximately 25 days (Crits-Christoph et al., 2008). As regards the use of opioids, in heroin-dependent subjects no significant differences in striatal DAT transporter availability versus controls have been found (Cosgrove et al., 2010). On the contrary, striatal DAT availability was significantly decreased in abusers of codeine-containing cough syrup frequently used by the general population (Hou et al., 2011). Furthermore, in abstinent heroin users some data suggest a long-term change of DAT availability, with a persistent lower DAT availability in the striatum after 6 months (Jia et al., 2005; Shi et al., 2008). Lastly, very little evidence is actually available about MDMA ("Ecstasy") influence on DAT levels (McCann et al., 2008), and no data have been collected on cannabis use.

In conclusion, the current or the past use of psychotropic substances is neglected in most of the imaging studies on depressed patients and scarce information is reported, mainly limited to the current use of nicotine and/or alcohol.

All the variables mentioned above have considerably influenced available results and, in this complexity, many other methodological differences, such as rating procedures (in the majority of studies the 17-item HAM-D have been used, but the cut-off scores were different) as well as scan protocols, probably played an additional role in confounding data interpretation.

An adequate knowledge on the role of pre-synaptic dopaminergic activity (trait versus state) or its predictive value in the pathophysiology of major depression requires additional investigations as well as rigorous methodologies.

3.1. Hypotheses about DAT role in depression

In light of the conflicting results, we could only formulate some preliminary hypotheses about the role of DAT in the pathophysiology of depression.

An altered DAT availability may represent a striatal-mediated dysregulation of cortical and limbic structures, thus reflecting affective and psychomotor changes that occur in depression (Meyer et al., 2001; Newberg et al., 2007a). Indeed, the striatum receives inputs from the cortex and the limbic system (i.e., the amygdala) and projects back to the cortex; these pathways modulate mood and behaviour. Therefore, alterations in striatal dopamine in depressed patients could impair cortico-striatal circuits disrupting limbic input back to the cortex (Drevets, 2000).

It has been hypothesized that a greater DAT density, reported in ^{99m}Tc-TRODAT-1 studies, may compensate for a diminished extraneuronal dopamine concentration (Amsterdam et al., 2012; Brunswick et al., 2003; Hsieh et al., 2010; Newberg et al., 2007a; Yang et al., 2008b). However, it is not possible to rule out that the greater DAT density acts as a compensatory clearing mechanism for excessive central dopamine concentrations.

Authors who reported a decrease in striatal DAT density during depression interpreted their data as indicative of a down-regulation of DAT secondary to lower dopamine concentrations in the synaptic cleft (Meyer et al., 2001; Sarchiapone et al., 2006; Wu et al., 2011). Consistent with this hypothesis, several studies have shown a decrease in DAT density when dopamine is chronically depleted (Gordon et al., 1996; Kilbourne et al., 1992). On the other hand, another possible explanation of an altered DAT availability in depressed patients could be the loss of dopamine fibres or cells. Indeed, post-mortem studies in MDD showed alterations in density and size of neuronal and glial cells in frontal and limbic regions. In addition, post-mortem neurochemical studies in MDD reported alterations in dopaminergic receptors and transporters in the amygdala, a key brain structure involved in the integration of emotions and stress (Klimek et al., 2002).

Conversely, it is not possible to rule out a primary DAT defect that makes subjects susceptible to developing depression. Some evidence has stemmed from several genetic studies suggesting that the genetic profile of the dopaminergic system may determine vulnerability to major depression, through interaction with the environment (aan het Rot et al., 2009). In fact, it has been found that a polymorphism in the DA type 2 receptor gene influences the effect of past stressful life events on current mood (Elovainio et al., 2007).

In our opinion, the dopaminergic regulation itself may differ from individual to individual in depressed subjects and DAT levels can be reduced only in certain patients, according to the specific clinical profile (anhedonia/retardation, early/late onset, etc.). Interestingly, a lower availability of DAT has been reported in anhedonic depressed patients (Sarchiapone et al., 2006). This finding is in agreement with the well-known higher reward effect after oral D-amphetamine administration shown by severe depressed subjects with respect to patients with a milder form of depression. In fact, a functional MR imaging study demonstrated that depressed subjects had a markedly greater behavioural response to the rewarding effects of D-amphetamine and altered brain activation of the ventrolateral prefrontal cortex, orbitofrontal cortex, caudate, and putamen (Tremblay et al., 2005). All together, these observations lead to the conclusion that a reduction in DAT availability may be a trait marker of anhedonic depression, suggesting a possible role of DAT as specific therapeutic target in patients with high levels of anhedonia.

An intriguing perspective that could explain the conflicting results about the role of DAT and other markers (e.g. SERT), is the hypothesis of depression as a neurodevelopment disorder. In this context, we may speculate that different forms of depression could be caused by an abnormal brain maturation occurred in different stages of development. Histofluorescence for dopamine and serotonin has been found in human foetuses as early as of 3 months gestation (Nobin and Bjorklund, 1973). This represents a critical period of gestation characterized by a dynamic spatio-temporal neuronal migration and differentiation. Therefore, an interplay between genetic background and environmental factors such as viral infection, toxins and stress may lead to abnormal wired brains characterized by different positioning and availability of DAT and SERT in depressed patients.

3.2. Suggestions for future research

We have outlined a list of major issues and also suggest some standardized procedures in collecting clinical and imaging data on major depressed patients (see Table 2) with the aim of delineating a possible "modus operandi" that could be a proposal for neuroreceptor studies on major depression. Such an approach has already led to remarkable developments in the field of neuroimaging studies, by defining a standard operating procedure (SOP) shared by consortia performing multicenter studies on large samples of patients (for more information see http://www.imagen-europe.com/en/consortium.php; or http://enigma.loni.ucla.edu/about/).

Firstly, as widely discussed, a fundamental issue of imaging studies on major depression is the heterogeneity of diagnosis. In addition to a categorical approach according to DSM criteria, using semi-structured interviews (SCID-I or MINI-Interview), clinical specifiers should also be reported and any axis I and II comorbidity should be highlighted for each patient. Moreover, it is advisable to enrol subjects who do not present comorbidity with other psychiatric disorders, such as schizoaffective disorder, dysthymia,

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Table 2
Suggestions for neuroimaging studies on depression.

1) Diagnosis heterogeneity: combining the categorical diagnosis of major depression along with appropriate dimensional diagnosis;
2) Choice of specific radioligands (e.g. [^{99m}Tc]TRODAT-1);
3) Sampling drug-naïve patients;
4) Exclusion of patients with current or past use of substances of abuse;
5) Harmonizing the use of appropriate rating scales: (e.g. HAMD-17, MADRS, SHAPS, DRRS, AQ);
6) Control for genetic polymorphisms: use of imaging – genetic techniques;
7) Monitoring clinical course variables: illness length, episode duration, lifetime number of episodes.

Abbreviations: HAMD-17 (*Hamilton Depression Rating Scale – 17 items*); MADRS (*Montgomery–Asberg Depression Rating Scale*); SHAPS (*Snaith–Hamilton Pleasure Scale*), DRRS (*Depression Retardation Rating Scale*); AQ (*Aggression Questionnaire*); [^{99m}Tc]TRODAT-1 (*^{99m}Tc][2[[2-[[[3-(4-chlorophenyl)-8-methyl-8a2abicyclo[3.2.1]oct-2-yl]-methyl](2-mercaptoethyl)amino]ethyl]amino]ethance-thiolato(3-)-N2,N2′,S2,S2′]oxo-[IR-(exo-exo)]*).

substance abuse, attention deficit disorder, anxiety disorders, mental retardation, etc. An accurate dimensional evaluation should be encouraged through specific psychometric instruments assessing the major psychopathological dimensions involved in depressive symptomatology, such as anhedonia, psychomotor retardation, aggressiveness, etc.

Secondly, the choice of the radioligand plays a key role in the analysis of data (see Table 3). Hence, it would be desirable to consider highly specific tracers in the case of dopamine transporter, such as [^{99m}Tc]TRODAT-1, ^{123}I-FP-CIT and [^{11}C]RTI-32 PET. The specificity of the radioligand, together with the semi-quantification method (advanced automated procedures or voxel-based statistical analysis are preferred due to a better reproducibility,) will allow more accurate results on DAT availability (Badiavas et al., 2011; Djang et al., 2012; Tatsch and Poepperl, 2012). Apart from the quantitative approach itself, standardization of the acquisition and reconstruction protocols may have a crucial role in delivering data which might be comparable.

Thirdly, future research requires a specific focus both on the use of drugs and current or past use or abuse of substances. In particular, for each patient it would be desirable to collect detailed information concerning all psychotropic substances (including nicotine, caffeine, etc.) taken in the past, the duration of use and the time of last administration. In addition to clinical and imaging results, all these data would have to be considered in statistical analysis as confounding factors.. Moreover, it would be necessary to separate drug-naïve patients, drug-free patients and subjects with no current or past substance use or abuse including alcohol and nicotine, which could be the most suitable cases for potential meta-analytic approaches.

Fourthly, it would be suitable to harmonize the use of appropriate rating scales. The 17-item-HAMD, widely employed in both clinical trials and imaging research on major depression, could be implemented as a golden standard for assessing depression severity. In order to investigate the relationship between clinical severity and imaging data more accurately, it would be appropriate to combine other rating tools, such as the Montgomery–Asberg Depression Rating Scale (MADRS) or other instruments mainly focused on the assessment of psychopathological dimensions (e.g. the Snaith–Hamilton Pleasure Scale – SHAPS, the Depression Retardation Rating Scale – DRRS, the Aggression Questionnaire – AQ, etc.).

Fifthly, other important clinical variables have to be considered, including longitudinal course specifiers and severity/psychotic/remission specifiers for the current episode, according to the DSM criteria. In particular, for each patient, it would be desirable to collect detailed information concerning major depressive episode duration, duration since diagnosis, lifetime number of MDE episodes and resistance to treatment (e.g. patients who did not respond satisfactorily to one or more optimally delivered treatments) (Rush et al., 2003). As a result, all these variables should also be taken into account in statistical analysis.

Moreover, in future studies on DAT imaging special attention should be focused also on genetic polymorphisms of DAT, and its relationship with the neuroimaging pattern. In fact, a reduction of DAT density was preliminarily found in 9-repeat/10-repeat heterozygotic carriers versus 10-repeat homozygous individuals (Heinz et al., 2000). Martinez et al. did not find any significant association between the variable number of tandem repeats polymorphism (VNTR) and DAT density (Martinez et al., 2001) whereas, more recently, a polymorphism of the 3′ untranslated region of the DAT gene (SLC6A3) has been associated with a greater availability of striatal DAT of the 9-repeats allele carriers (van de Giessen et al., 2009; van Dyck et al., 2005). In light of this, genetic background knowledge combined with imaging (imaging-genetic techniques) will also yield a better understanding of the relationship between clinical data and neuroimaging pattern of depressed patients.

Table 3
Pro and cons of radioligands used for DAT research in depressed subjects.

Tracer	Pro	Cons	Suitable for DAT research
[^{99m}Tc]TRODAT-1	High affinity and specificity for DAT; The only available technetium labelled Radioligand; Lack of thyroid uptake; Widely available and cheap ^{99m}Tc radiochemistry.	Target-to-background ratio is lower for [^{99m}Tc] TRODAT-1 than for [^{123}I]-labelled radioligands.	Yes
[^{123}I]-β-CIT	One of most frequently used DAT tracer in the past.	Not specific for DAT binding; High affinity for serotonin and norepinephrine transporters; Distribution of ^{123}I isotopes; Expensive and not readily available on-site.	No
[^{123}I]nor-β-CIT	None	Noradrenergic transporter (NORT) binding; More serotonin-specific (SERT); Distribution of ^{123}I isotopes; Expensive and not readily available on-site.	No
[^{123}I]-FP-CIT	High affinity for DAT; Commercially available (DaTSCAN) for routine clinical use; Higher selectivity for DAT and faster kinetics than [^{123}I]-β-CIT.	Affinity for serotonin transporter (SERT); Distribution of ^{123}I isotopes; Expensive and not readily available on-site.	Yes
[^{11}C]RTI-32	PET radioligand; High affinity for DAT.	Nanomolar affinity for the noradrenaline (NORT) and serotonin (SERT) transporters.	Yes

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In conclusion, all the above mentioned points certainly require further discussion among researchers and clinicians. In our opinion both researchers and clinicians have to develop a shared approach to achieve a definite awareness of the numerous factors involved in the neurobiological pathways of major depression.

Standardized procedures are also necessary in order to merge all data from the literature and to perform further analysis, through a meta-analytic approach, on larger samples that would be more representative of the depressed patient population.

Finally, standardized procedures will also allow further investigation of both clinical dimensions and particular psychopathological profiles that could be related to different pathophysiological pathways.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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