Dopaminergic System Alteration in Anxiety and Compulsive Disorders: A Systematic Review of Neuroimaging Studies

Mei-Xue Dong¹, Guang-Hui Chen² and Ling Hu*¹

¹ Department of Neurology, Hubei General Hospital, Renmin Hospital of Wuhan University, Wuhan, China, ² Department of Pharmacy, Hubei General Hospital, Renmin Hospital of Wuhan University, Wuhan, China

Objective: The dopaminergic system is involved in many psychiatric disorders as a GABAergic, serotonergic, and glutamatergic system. A systematic review and meta-analysis was performed to elucidate the alteration of the dopaminergic system in anxiety and compulsive disorders.

Methods: The databases of Pubmed, Embase, and ScienceDirect were searched and articles reporting the involvement of the dopaminergic system in patients with anxiety disorder and obsessive compulsive disorder (OCD) were recognized. The key research data were extracted from the included articles and standardized mean differences were calculated using meta-analyses if there were more than two studies with obtainable data. Sensitivity analyses were further performed to detect the stability of results, and the qualities of all the included studies were assessed using the Newcastle Ottawa scale.

Results: Finally, we identified 8 and 11 studies associated with anxiety disorder and OCD for further analysis, respectively. Most consistently, the striatal dopamine D₂ receptor (D₂R) of OCD patients had decreased while no significant correlation was found between striatal D2R and disease severity. The striatal dopamine transporter (DAT) had not been significantly altered in both the anxiety disorder and OCD patients. The heterogeneity values from the meta-analyses were extremely high while those results remained stable after sensitivity analyses. Inconsistent data were found in the striatal D₂R of patients with anxiety disorder. Limited data had suggested that dopamine synthesis increased in most regions of the cerebral cortex and cerebellum in OCD patients.

Conclusions: The most convincing finding was that the D₂ receptor decreased in patients with obsessive compulsive disorder. The dopamine transporter may have no relationship with anxiety and compulsive disorder.

Keywords: anxiety, obsessive compulsive disorder, systematic review, dopamine, neuroimaging
INTRODUCTION

Anxiety and compulsive disorder has been recognized as one of the most prevalent psychiatric disorders in the Chinese mainland and its prevalence has ranged from 24.47 to 41.12% (Guo et al., 2016). This broad-spectrum disorder includes generalized anxiety disorder (GAD), non-specific anxiety disorder, panic disorder with or without agoraphobia, social anxiety disorder (SAD), specific phobia, post traumatic stress disorder (PTSD), and obsessive compulsive disorder (OCD) according to the former diagnostic criteria, while OCD and PTSD have been listed as independent diseases according to the recent Diagnostic and Statistical Manual of Mental Disorders, version V (DSM-V).

Various neurotransmitters have been implicated in the pathophysiology of anxiety and compulsive disorder including dopamine (Plavén Sigray et al., 2016), serotonin (Nikolaus et al., 2016), glutamate (Spencer et al., 2014), and γ-aminobutyric acid (GABA) (Mohler, 2012). A meta-analysis of $^1$H magnetic resonance spectroscopy (MRS) reported that no significant differences in GABA levels were found in panic disorder patients (Schür et al., 2016) while the GABA(A) receptor was reported to decrease throughout the mesolimbocortical system in anxiety disorder (Nikolaus et al., 2014). Another systematic review found that patients with anxiety-related disorder displayed a significant reduction in the serotonin transporter in the thalamus, amygdala, and hippocampus, reductions of 5-HT$_{1A}$ receptors in the frontal cortex, cingulate, midbrain, hippocampus, amygdala, and insula, and a significant elevation of 5-HT$_{2A}$ receptors in the temporal cortex (Nikolaus et al., 2016). The increase of striatal Glx (combination of glutamate, glutamine, and GABA) in OCD patients was also concluded in a review (Naaijen et al., 2015).

There is sufficient evidence for the involvement of the dopaminergic system in psychiatric disorders such as schizophrenia (Horga et al., 2016), major depression disorder (Wooten et al., 2015), bipolar disorder (Yatham et al., 2002), attention deficit hyperactive disorder (ADHD) (Badgaiyan, 2016), anorexia nervosa (Broft et al., 2015), Tourette syndrome (Steeves et al., 2010), and autism (Nakamura et al., 2010). Dopamine is an important neurotransmitter in the central nervous system and is known to regulate human emotions and cognitive abilities, including feeling, thinking, understanding, and reasoning in physiological processes (Pine et al., 2010). A variety of approaches have been applied to determine the role of the dopaminergic system in the brain, however, positron emission tomography (PET) and single photon emission computed tomography (SPECT) are the only methods used to explore the dopaminergic system directly in vivo. We can now assess dopamine synthesis, release, synaptic vesicular transporters, dopaminergic receptors, and DAT in vivo using PET or SPECT with a radiotracer such as $^{[18]}$F-DOPA, $^{[11]}$C-DOPA, $^{[11]}$C-DTBZ, $^{[123]}$I-FP-CIT, $^{[123]}$I-β-CIT, $^{[11]}$C-PE2i, $^{[11]}$C-CFT, $^{[99m]}$Tc-TRODAT, $^{[11]}$C-SCH 23390, $^{[11]}$C-NNC 112, $^{[123]}$I-IBZM, $^{[11]}$C-RAC, and $^{[18]}$F-fallypride (Fusar-Poli and Meyer-Lindenberg, 2013). Taking advantage of these examinations, dopaminergic system alteration has been gradually cleared in many psychiatric disorders such as schizophrenia (Fusar-Poli and Meyer-Lindenberg, 2013), ADHD (Fusar-Poli et al., 2012), and major depression disorder (Li et al., 2015).

We have performed a number of studies on affective diseases and Parkinsonism-related disorders and found that the dopaminergic system might play an important role in anxiety disorders (Dong et al., 2018a,b). Nearly half of patients with Parkinson’s disease (PD) suffer serious anxiety disorders while the dopaminergic system is confirmed to be the main pathological footstone of PD. Dopamine agonist pramipexole was also reported to alleviate mood disorder in PD patients. There are a number of studies that have focused on the dopaminergic system in anxiety and compulsive disorder but the results were inconsistent with each other. The lack of conformity and fragmentary nature of these results prompted us to reassess the dopaminergic system in patients with anxiety and compulsive disorder. Thus, we performed this systematic review and meta-analysis to elucidate dopaminergic system alteration in anxiety and compulsive disorder.

METHODS

We carried out the systematic review and meta-analysis following the guidelines recommended by PRISMA statements and the protocol that has already been registered with PROSPERO (CRD42016046788) (Moher et al., 2010).

Data Sources and Searches

Pubmed, Embase, and ScienceDirect were searched without restrictions of language, publication type, or publication period. The detailed search strategy is shown in Table 1. Briefly, our search criteria included articles that had words related to each of the following three categories in the title or abstract: (i) anxiety-related disorder or OCD; (ii) DAT, dopamine receptor, dopamine synthesis, or dopamine release; (iii) PET or SPECT in vivo studies. This search retrieved all articles through to August 20, 2020. In addition, a backward search of bibliographic references from the identified articles was performed and articles were examined to verify that all relevant articles were included in this article.

Study Selection

Each article obtained from the search strategy was then reviewed to determine its inclusion or exclusion according to the following criteria. The included articles should compare related psychiatric patients with healthy controls. In the meanwhile, dopaminergic systems, including dopamine synthesis, dopamine release, dopaminergic receptors, or DAT, should be determined by PET or SPECT in vivo between the two groups. The exclusion criteria were reviews, case reports, protocols, animal studies, repeated reports from the same research group, and any other research purposes.

Data Extraction

Finally, all the included articles were reviewed by two skillful reviewers devoted to psychiatric disorders (MXD and LH). We recorded the following variables from each article: article information, characteristics of subjects, diagnostic criteria,
disease severity scale score, assessment method, reference region, region of interest (ROI), and dopaminergic findings. A third reviewer (GHC) then reviewed all the articles and extracted data to check for any errors. Information regarding the direction and significance of the dopaminergic system (including mean values and standard deviation values) of ROI were then used for further analysis.

### Statistical Methods

A meta-analysis was conducted to merge the effect size together if there were more than two studies with obtainable data. The process of statistical analysis was as described before (Dong et al., 2016). Briefly, standardized mean differences (SMDs) were calculated to assess the changes of each efficacy outcome for continuous measures and combined

---

**TABLE 1** | Search strategy of database.

| Data source  | Search strategy                                                                 | Total count |
|--------------|---------------------------------------------------------------------------------|-------------|
| Pubmed       | (((((((((((((anxiety[Title/Abstract]) OR phobia[Title/Abstract]) OR panic[Title/Abstract]) OR agoraphobia[Title/Abstract]) OR ptsd[Title/Abstract]) OR gad[Title/Abstract]) OR ocd[Title/Abstract])) OR obsessive compulsive disorder[Title/Abstract]) OR impulsive[Title/Abstract]) AND (((dopamine[Title/Abstract]) OR dopaminergic[Title/Abstract]) OR dnergic[Title/Abstract]) AND (((spect[Title/Abstract]) OR spet[Title/Abstract]) OR pet[Title/Abstract]) OR positron emission tomography[Title/Abstract]) OR single photon emission computed tomography[Title/Abstract]) OR single photon emission tomography[Title/Abstract]) | 255         |
| Embase       | "anxiety":ab OR "phobia":ab OR "panic":ab OR "agoraphobia":ab OR "gad":ab OR "ocd":ab OR "obsessive compulsive disorder":ab OR "impulsive":ab AND ("spect":ab OR "spet":ab OR "pet":ab OR "single photon emission computed tomography":ab OR "positron emission tomography":ab OR "single photon emission tomography":ab) AND ("dopamine":ab OR "dopaminergic":ab OR "dnergic":ab) | 446         |
| ScienceDirect| [abstract (anxiety) or abstract (phobia) or abstract (panic) or abstract (agoraphobia) or abstract (gad) or abstract (ocd) or abstract (obsessive compulsive disorder) or abstract (impulsive) or abstract (spect) or abstract (spet) or abstract (pet) or abstract (single photon emission computed tomography) or abstract (positron emission tomography)] and [abstract (dopamine) or abstract (dopaminergic) or abstract (dnergic)] | 79          |

---

**FIGURE 1** | PRISMA flow diagram of this systematic review and meta-analysis.
### TABLE 2 | Studies assessing dopaminergic system using PET or SPECT in patient with anxiety and compulsive disorder.

| Study                      | Subjects                                      | Diagnostic criteria                      | Method                          | RR     | ROI                  | Dopaminergic system findings                                                                 |
|----------------------------|-----------------------------------------------|------------------------------------------|---------------------------------|--------|----------------------|---------------------------------------------------------------------------------------------|
| **Anxiety disorder (8)**   |                                               |                                          |                                 |        |                      |                                                                             |
| Tiilinen et al. (1997)      | 11 SAD (age 40.5 ± 5.3, 3 males); 28 controls (age 39.6 ± 12.3, 19 males) | DSM-III-R SAD; CDSI 5.09 ± 0.64; Drug free | SPECT, [¹²³I]-β-CIT            | White matter | Striatum (basal angula) | DAT decreased in striatum (10.05 ± 1.20 vs. 11.64 ± 1.39, p < 0.001); No significant correlation between disease severity and striatal DAT |
| Van der Wee et al. (2008)  | 12 SAD (age 39.4 ± 12.6, 7 males); 12 controls (age 33.0 ± 9.5, 7 males) | DSM-IV SAD; LSAS 7.36 ± 13.7; Drug naive | SPECT, [¹²³I]-β-CIT            | Cerebellum | Striatum | DAT increased in striatum (7.30 ± 0.98 vs. 5.47 ± 1.37, p = 0.011); No significant correlation between LSAS score and striatal DAT |
| Maron et al. (2010)        | 7 current PD (35.7 ± 16.8, 0 male); 7 PD in remission (33.4 ± 14.3, 0 male); 7 controls (35.1 ± 5.3, 0 male) | DSM-IV PD; PDSS (8.9 ± 2.3); Drug free (>4 m) | SPECT, [¹²³I]-β-CIT            | Cerebellum | Striatum | DAT increased in striatum of remitted PD (2.72 ± 0.27, p = 0.04), didn’t change in striatum of current PD compared with control (2.21 ± 0.29 vs. 2.43 ± 0.17, p = 0.12); There was an inverse relationship between striatal DAT in total group and the PDSS score, no correlation exist between these two subgroups |
| Lee et al. (2015)          | 12 GAD (age 37.1 ± 12.6, 4 males); 12 controls (age 37.2 ± 12.9, 4 males) | DSM-IV GAD; HAM-A; Drug free (>3 m) | SPECT, [⁹⁹mTc]-TRODAT-1        | Occipital cortex | Striatum | DAT decreased in striatum (1.53 ± 0.46 vs. 2.01 ± 0.31, p = 0.004) |
| Hjorth et al. (2019)       | 27 SAD (age 31.1 ± 10.32, 17 males); 43 controls (age 32.81 ± 11.56, 23 males) | DSM-IV SAD; LSAS-SR 84.96 ± 20.37; Drug free (>3 m) | PET, [¹¹C]-PE2I                | Cerebellar gray matter | Amygdala, hippocampus, caudate, and putamen; There was a positive correlation between disease severity and DAT availability in the amygdala, hippocampus, and putamen |
| Schneier et al. (2009)     | 15 SAD (age 31.1 ± 6.6); 12 controls (age 30.9 ± 8.1) | DSM-IV SAD; LSAS 78.6 ± 19.2; Drug free (several months) | SPECT, [¹²³I]-β-CIT, [¹⁰⁰mTc]-β-CIT; PET, [¹¹C]-RAC; | Occipital region | Striatum | DAT did not differ in striatum (7.69 ± 1.12 vs. 7.62 ± 0.91, p = 0.87), D₂R did not differ at baseline (13.0 ± 3.7 vs. 13.8 ± 3.2, p = 0.58); No significant correlation between LSAS score and striatal DAT, D₂R and dopamine release |
| Schneier et al. (2000)     | 10 SAD (age 32.5 ± 10.4, 5 males); 10 controls (age matched) | DSM-IV SAD; LSAS 84.96 ± 20.37; Drug free (>1 y) | SPECT, [¹²³I]-IB2M             | Occipital region | Striatum | D₂R decreased in striatum (93.8 ± 29.8 vs. 133.5 ± 38.2, p = 0.02); No significant correlation between LSAS score and striatal D₂R |
| Plavén-Sigray et al. (2017)| 12 SAD (age 33.82 ± 11.55); 16 controls (age 37.82 ± 15.22) | DSM-IV SAD; LSAS-SR 63.73 ± 10.48; Drug free | PET, [¹¹C]-FLB457             | Lateral prefrontal cortex, medial frontal cortex, orbitofrontal cortex, anterior cingulated cortex, insula, amygdala, hippocampus | Cerebellum | D₂R increased in the orbitofrontal cortex (0.99 ± 0.28 vs. 0.76 ± 0.27, p = 0.03), no significant differences in the other regions; There was a positive correlation between LSAS-SR summed scores and orbitofrontal cortex D₂R |

(Continued)
| Study | Subjects | Diagnostic criteria | Method | RR | ROI | Dopaminergic system findings |
|-------|----------|---------------------|--------|----|-----|-----------------------------|
| **Obsessive compulsive disorder (11)** | | | | | | |
| Kim et al. (2003) | 15 OCD (age 28.53 ± 10.91, 11 males); 19 controls (age 30.53 ± 8.82, 11 males) | DSM-IV-Korean version; Y-BOCS 15.27 ± 3.86; Drug free (>4 w) | SPECT, [123]I-IPT | Occipital cortex | Striatum (basal ganglia) | DAT increased in the right basal ganglia (6.84 ± 2.82 vs. 4.61 ± 1.06; p = 0.009) while it tends to increase in the left basal ganglia (6.74 ± 3.36 vs. 4.85 ± 1.13, p = 0.06); No significant correlation between Y-BOCS score and striatal DAT | |
| Van der Wee et al. (2004) | 15 OCD (age 31.4 ± 9.0, 11 males); 15 controls (age 32.0 ± 9.5, 11 males) | DSM-IV; Y-BOCS 23.4 ± 4.2; Drug naive | SPECT, [123]I-β-CIT | Cerebellum | Striatum (caudate, putamen) | DAT increased in left caudate (6.86 ± 0.64 vs. 5.99 ± 0.78, p = 0.004), right caudate (6.78 ± 0.67 vs. 6.16 ± 0.85, p = 0.04), left putamen (8.00 ± 0.74 vs. 7.04 ± 0.79, p = 0.006), and right putamen (7.97 ± 0.89 vs. 7.16 ± 1.23, p = 0.05); No significant correlation between DAT and Y-BOCS score | |
| Hesse et al. (2005) | 15 OCD (age 32.1 ± 11.7, 8 males); 10 controls (40 ± 13.2, 7 males) | ICD-10; Y-BOCS 25.3 ± 8.8; Drug naive | SPECT, [123]I-IBZM | Occipital cortex | Striatum Thalamus Midbrain Brainstem | DAT decreased in striatum (13.2 ± 1.6 vs. 14.9 ± 3.3, p = 0.001), thalamus/hypothalamus (4.2 ± 0.9 vs. 4.9 ± 0.8, p = 0.026), midbrain (2.5 ± 0.6 vs. 3.3 ± 0.8, p = 0.008), and brainstem (1.7 ± 0.6 vs. 2.4 ± 0.7, p = 0.014); No significant correlation between DAT and Y-BOCS score | |
| Hoexter et al. (2013) | 41 OCD (age 30.6 ± 11.3); 32 controls (age matched) | DSM-IV; Y-BOCS; Drug naive | SPECT, [99mTc]-TRODAT-1 | Cerebellum | Striatum (anterior putamen) | DAT decreased in the right anterior putamen (2.05 ± 0.36 vs. 2.24 ± 0.37, p = 0.031) and a statistical tendency in the left anterior putamen (2.04 ± 0.40 vs. 2.27 ± 0.55, p = 0.071) | |
| Oller et al. (2009) | 7 OCD (age 40.0 ± 13.9, 4 males); 7 controls (age 40.3 ± 12.3, 4 males) | DSM-IV; Y-BOCS 22.1 ± 7.6; Drug naive (>10 d) | PET, [11C]-SCH23390 | Cerebellum | Striatum | DAT increased in caudate compared with controls (0.59 ± 0.06 vs. 0.88 ± 0.06, p < 0.05), and it also decreased in putamen (0.89 ± 0.06 vs. 1.14 ± 0.06, p < 0.05); No significant correlations between DAT and Y-BOCS score | |
| Oller et al. (2010) | 7 OCD (age 40.0 ± 13.9, 4 males); 7 controls (age 40.3 ± 12.3, 4 males) | DSM-IV; Y-BOCS 22.1 ± 7.6; Drug naive (>10 d) | PET, [11C]-SCH23390 | Cerebellum | Anterior cingulate cortex | DAT increased in left anterior cingulate compared with controls (0.14 ± 0.04 vs. 0.29 ± 0.01, p < 0.05), and it also decreased in the right (0.13 ± 0.03 vs. 0.25 ± 0.02, p < 0.05); High negative correlations were found between DAT and Y-BOCS score | |
| Denys et al. (2004) | 10 OCD (age 36.4 ± 12, 3 males); 10 controls (age 33.7 ± 10, 3 males) | DSM-IV; Y-BOCS 25.9 ± 6.5; 2 drug naive, 8 drug free (>1 m) | SPECT, [123]I-IBZM | Cerebellum | Striatum (caudate, putamen) | DAT decreased in left caudate nucleus (p = 0.016) while it decreased not significantly in right caudate, left and right putamen; No significant correlation between Y-BOCS score and DAT | |

(Continued)
into a pooled SMD. If data were measured several times in different parts of the same brain region in one individual, a weighted average and standard deviation were calculated according to the following formulas merged N = \sum_{i=1}^{n} \frac{N_i + N_2}{2}

\text{merged mean} = \frac{\sum_{i=1}^{n} \left( \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2} \right)}{N_1 + N_2},

\text{merged standard deviation} = \sqrt{\frac{\sum_{i=1}^{n} \left( N_1 - 1 \right) \frac{SD_1^2}{N_1} + \left( N_2 - 1 \right) \frac{SD_2^2}{N_2} + \left( N_1 + N_2 \right) \left( M_1^2 + M_2^2 - 2M_1M_2 \right)}{(N_1 + N_2 - 1) \cdot (N_1 + N_2)}}.

Heterogeneity across studies was assessed using \chi^2 test and expressed using I^2 statistic values. An I^2 of <25%, <50%, <75%, and ≥75% represented low, moderate, high, and extremely high heterogeneity, respectively. Sensitivity analyses were conducted using the leave-one-out method.

Data were analyzed using RevMan5.4 (Cochrane Information Management System).

**RESULTS**

**Literature Search Results**

The detailed flowchart of the study selection is shown in Figure 1. A total of 781 records were initially identified and 507 records were left after duplicate records were removed; of these, 473 records were then excluded by title/abstract screening. Of the 34 remaining relevant records, 15 records were further excluded as they were protocol reports, repeated reports from the same research team, a study without healthy controls, or had another research purpose. Thus, 19 studies were finally included in this review (Tiitonen et al., 1997; Schnee et al., 2000, 2008, 2009; Kim et al., 2003; Denys et al., 2004, 2013; Van der Wee et al., 2004, 2008; Hesse et al., 2005, 2010; Perani et al., 2008; Olver et al., 2009, 2010; Maron et al., 2010; Hoexter et al., 2013; Hsieh et al., 2014; Lee et al., 2015; Plavén-Sigray et al., 2017; Hjorth et al., 2014; Lee et al., 2015; Plavén-Sigray et al., 2017; Hjorth et al.,...
2019). We then aggregated these studies by psychiatric disorders, including anxiety disorder and obsessive compulsive disorder. The characteristics of each study are exhibited in Table 2. The Newcastle Ottawa scales of all the included studies are shown in Table 3.

### Dopaminergic System in Patients With Anxiety Disorder

There were a total of eight studies focusing on the dopaminergic system in patients with anxiety disorder. The mean age of subjects ranged from 30 to 40 years old without statistically significant differences, and no specific pattern of age emerged among these studies. Striatal DAT was reported in six studies and the results were different from each other. A meta-analysis was conducted and no statistically positive effect was found as the total pooled SMD was 0.09 [95% confidence interval (CI), −1.08 to 1.27] (Figure 2A). The heterogeneity was extremely high ($I^2 = 89\%$) while the result remained stable through sensitivity analyses (Table 4). All of them reported no significant correlation between striatal DAT and disease severity. Only one study (Hjorth et al., 2019) assessed an extrastriatal dopamine transporter and found that the increased dopamine transporter in the amygdala and hippocampus was positively correlated with disease severity. Two studies (Schneider et al., 2000, 2009) from the same team determined the striatal dopamine $D_2$ receptor ($D_2R$) using different radiotracers while the results were contradictory. They also found that dopamine release had not changed in anxiety patients (Schneider et al., 2009). Another study (Plaven-Sigray et al., 2017) indicated that $D_2R$ had increased in the orbitofrontal cortex using a high-affinity $D_2R$ radiotracer whilst a positive correlation was found between disease severity and orbitofrontal cortex $D_2R$.

### Dopaminergic System in OCD Patients

A total of 11 studies examined the dopaminergic system in OCD patients. The mean age of OCD patients ranged from 28 to 40 years old, and the controls were age-sex matched with those patients. Striatal DAT was determined in four studies and all the means were merged together using a meta-analysis (Figure 2B). The overall result showed no significant change and the total pooled SMD was 0.12 (95% CI, −0.69 to 0.94). Although the heterogeneity was extremely high ($I^2 = 83\%$), the result remained stable through sensitivity analyses (Table 4). No significant correlation was claimed by these studies between DAT and disease severity. A research team indicated that the dopamine $D_1$ receptor ($D_1R$) had decreased in both the striatum and anterior cingulate cortex separately in two articles (Olver et al., 2009, 2010). High negative correlation was found between the total score of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and $D_1R$ in the anterior cingulate cortex but not in the striatum. Four studies (Denys et al., 2004, 2013; Perani et al., 2008; Schneider et al., 2008) determined striatal $D_2R$ but only three studies with obtainable data could be merged using a meta-analysis (Figure 2C). The merged result was statistically significant and
the total SMD was \(-0.68\) (95% CI, \(-1.23\) to \(-0.12\)). The heterogeneity was mild ($I^2 = 0\%$) while the result was unstable through sensitivity analyses (Table 4). A study (Denys et al., 2013) that was excluded in the meta-analysis also claimed a decrease of $D_2$R. Meanwhile, there was no significant correlation between the Y-BOCS score and $D_2$R. In the meantime, one study (Denys et al., 2013) assessed dopamine release in OCD patients and no changes of $D_2$R could be found after an injection of amphetamine in the striatum compared with controls. A study (Hsieh et al., 2014) indicated that dopamine synthesis increased throughout the brain, including the left frontal premotor cortex, left posterior cingulate gyrus, left cuneus, left lingual gyrus, right cuneus and precuneus, right lingual gyrus, right middle temporal gyrus, left cerebellum, and right cerebellum.

**DISCUSSION**

The dopaminergic system mainly consists of nigrostriatal, mesocortical, mesolimbic, and tuberoinfundibular pathways (Hou et al., 2014). Dopamine is synthesized by dopaminergic neurons in the substantia nigra pars compacta, ventral tegmental area, and arcuate and periventricular nucleus of the hypothalamus (Cortes et al., 2016). After being released into the synaptic cleft, it binds with dopamine receptors 1–5 (mainly $D_1$R and $D_2$R) to exert excitatory or inhibitory signaling. The dopamine in the synaptic cleft can be dissolved by catechol-O-methyltransferase and monoamine, and its level can also be modulated by a dopamine transporter (Figure 3). The involvement of the dopaminergic system in some psychiatric disorders has already been elucidated in detail and might shed light on further drug design strategies (Leggio et al., 2016).

Anxiety and compulsive disorder is among the most common psychiatric disorders, with a lifetime prevalence between 17 and 69% (Kessler et al., 2007). An ongoing issue is that the disorder is under-diagnosed and most patients never receive any treatment. Currently, diagnosis lacks repeatable and objective evidence, and is mainly dependent on the professional skills of psychiatrists and some clinical psychiatric scales. Serotonin reuptake inhibitors

---

**FIGURE 2** | Forest plots of SMDs in the meta-analysis. (A) DAT had not altered in patients with anxiety disorder (95% CI of SMD, \(-1.49\) to \(1.59\)) and the heterogeneity was extremely high ($I^2 = 91\%$); (B) DAT had not altered in OCD patient (95% CI of SMD, \(-0.69\) to \(0.94\)) while the heterogeneity was extremely high ($I^2 = 83\%$); and (C) dopamine $D_2$ receptors had decreased in OCD patient (95% CI of SMD, \(-1.23\) to \(-0.12\)) and the heterogeneity was mild ($I^2 = 0\%$). SMD, standard mean deviation; DAT, dopamine transporter; OCD, obsessive compulsive disorder.
and serotonin norepinephrine reuptake inhibitors are usually used as part of the preferred initial treatment (Katzman et al., 2014) with response rates in the range of 30–50% (Reinhold and Rickels, 2015). We have performed a number of studies about this issue before (Dong et al., 2017a,b; Dong et al., 2018a; Chen et al., 2020; Hu et al., 2020). The main aim of this study was to assess whether dopaminergic dysregulation can be detected in anxiety and obsessive disorder with any degree of consistency and specificity. We hope to elucidate the mechanisms of these disorders for clinical diagnosis and further drug development.

Overall, the available studies were quite heterogeneous and often contradictory. Eight studies provided evidence of the dopaminergic system in anxiety patients and eleven studies focused on OCD patients. In the total 19 studies, 10 studies were about DAT, seven studies were about D2R, two studies were about D1R, two studies were about dopamine release, and only one study was about dopamine synthesis.

The alterations of DAT in patients with anxiety disorders were inconsistent with each other, although the same radiotracer and technique were used. In total, no alteration could be found during the meta-analysis. The primary discrepancy between these studies could have been due to their small sample sizes. Other possible reasons may be the methodological differences. Two studies administered the serotonin reuptake inhibitors citalopram (Tiihonen et al., 1997) or paroxetine (Van der Wee et al., 2008) to block [123I]-β-CIT from binding to serotonin transporters before a SPECT scan while another study did not (Schneier et al., 2009). Reference regions were different as well, including white matter, the cerebellum, and the occipital region. Structural MRI was also used to accurately identify regions of interest in a study (Van der Wee et al., 2008). All of these may partly explain the extremely high heterogeneity of striatal DAT. A recent study from Hjorth using PET (Hjorth et al., 2019) claimed that DAT of the amygdala and hippocampus had increased in 27 anxiety patients. Striatal D2R binding significantly decreased in a study using SPECT (Schneier et al., 2000), however, the result had changed when using another radiotracer (Schneier et al., 2009) performed by the same team. The researchers themselves mainly attributed it to the small sample size and not to methodological difference. They also did not find any change in dopamine release after an amphetamine injection. A recent study (Plavén Sigray et al., 2016) using PET with [11C]-FLB457 as the radiotracer found D2R had increased in the orbitofrontal cortex. However, this finding did not survive after correction for multiple comparisons. In short, no reliable evidence can confirm that the dopaminergic system has participated in anxiety disorders.

### Table 4

| Study omitted | SMD | Lower limit | Upper limit | p value |
|---------------|-----|-------------|-------------|---------|
| DAT of anxiety disorder | | | | |
| Lee et al. (2015) | 0.42 | −0.96 | 1.80 | 0.55 |
| Maron et al. (2010) | −0.26 | −1.48 | 0.96 | 0.68 |
| Schneier et al. (2009) | 0.12 | −1.47 | 1.71 | 0.88 |
| Tiihonen et al. (1997) | 0.47 | −0.79 | 1.74 | 0.46 |
| Van der Wee et al. (2008) | −0.27 | −1.43 | 0.89 | 0.65 |
| DAT of obsessive compulsive disorder | | | | |
| Hesse et al. (2005) | 0.37 | −0.62 | 1.36 | 0.46 |
| Hoexter et al. (2013) | 0.36 | −0.61 | 1.33 | 0.46 |
| Kim et al. (2003) | −0.14 | −0.98 | 0.70 | 0.74 |
| Van der Wee et al. (2004) | −0.09 | −1.03 | 0.86 | 0.86 |
| D2R of obsessive compulsive disorder | | | | |
| Denys et al. (2004) | −0.64 | −1.34 | 0.07 | 0.08 |
| Perani et al. (2008) | −0.67 | −1.36 | 0.02 | 0.06 |
| Schneier et al. (2009) | −0.71 | −1.38 | −0.05 | 0.03 |

SMD, standard mean difference; DAT, dopamine transporter; D2R, dopamine D2 receptor.
There were a total of four studies focusing on DAT in OCD patients and no alteration of DAT was found in OCD patients using a meta-analysis. D_2R of OCD was determined only in two studies from the same team (Olver et al., 2009, 2010). They found that D_2R had decreased in the striatum and anterior cingulate cortex. Only seven patients were included in the study so the result needs to be further confirmed. D_2R had decreased in OCD patients and mild heterogeneity existed. Dopamine release seemed to have no correlation with OCD, either. Only one study (Hsieh et al., 2014) including five patients with OCD determined dopamine synthesis, and it found that dopamine synthesis decreased throughout the brain.

Multiple neurotransmitter systems were involved in the mechanism of OCD according to former studies. It was reported that Glx had decreased in the anterior cingulate cortex while it increased in the caudate using MRS (Brennan et al., 2013; Naaijen et al., 2014). The serotonergic system had also been significantly altered, as reported in a comparative analysis (Nikolaus et al., 2016). The dopaminergic system may be regulated by the glutamatergic and serotonergic systems (Nikolaus et al., 2010).

From this research, we confirmed that striatal D_2R had decreased in OCD patients. It may be due to receptor internalization, increased levels of endogenous dopamine competing with the radiotracer, or a combination of both (Denys et al., 2013). A dopamine depletion study should be performed to assess whether endogenous dopamine was involved in OCD patients. Currently, serotonin remains the therapeutic target of neurotransmitters and selective serotonin reuptake inhibitors are the first-line drugs to treat OCD patients. However, those drugs can not function well in many patients and induce a number of side effects. Atypical antipsychotics are an important replacement therapy for some OCD patients. These drugs, including risperidone and aripiprazole, can activate D_2R as well as regulating the serotonergic system (Stein et al., 2012). Pramipexole, a dopamine D_2 R agonist widely used in PD patients, was also reported to be one of the most important drugs for depression in PD patients. It is worthwhile to explore the usage of these dopamine receptor agonists in OCD patients.

**CONCLUSION**

This is the first systematic review and meta-analysis to elucidate the dopaminergic system in anxiety and compulsive disorder. Studies about this issue are limited in number and contradictory. The most convincing finding is that striatal D_2R was decreased in OCD patients. Dopamine transporters may have no relationship with anxiety and compulsive disorder. The alteration of the dopaminergic system needs to be further confirmed by more repeatable, reliable, and large-sample size research.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

**AUTHOR CONTRIBUTIONS**

M-XD and LH conceived the study. The data analysis was performed by M-XD, G-HC, and LH. The manuscript was revised by M-XD and LH. All authors contributed to the article and approved the submitted version.

**FUNDING**

This research was supported by the Hubei Provincial Natural Science Foundation of China (2020CFB232) and the Fundamental Research Funds for the Central Universities (2042020k0056).

**REFERENCES**

Badgaiyan, R. (2016). Dynamic molecular imaging guides treatment options for attention deficit hyperactive disorder (ADHD). *J. Nuclear Med.* 57.

Brennan, B. P., Rauch, S. L., Jensen, J. E., and Pope, H. G. (2013). A critical review of magnetic resonance spectroscopy studies of obsessive-compulsive disorder. *Biol. Psychiatry* 73, 24–31. doi: 10.1016/j.biopsych.2012.06.023

Broft, A., Slifstein, M., Osborne, J., Kothari, P., Morim, S., Singleton, R., et al. (2015). Striatal dopamine type 2 receptor availability in anorexia nervosa. *Psychiatry Res.* 233, 380–387. doi: 10.1016/j.psychres.2015.06.013

Chen, G., Wang, Y., Li, Y., Zhang, L., and Dong, M. (2020). A novel hippocampus metabolite signature in diabetes mellitus rat model of diabetic encephalopathy. *Metab. Brain Dis.* 35, 895–904. doi: 10.1010/s11011-020-00541-2

Cortes, A., Moreno, E., Rodriguez-Ruiz, M., Canela, E. I., and Casado, V. (2016). Targeting the dopamine D3 receptor: an overview of drug design strategies. *Expert Opin. Drug Discov.* 11, 641–666. doi: 10.1080/17460441.2016.1185413

Denys, D., De Vries, F., Cath, D., Figee, M., Vulink, N., Veltman, D. J., et al. (2013). Dopaminergic activity in Tourette syndrome and obsessive-compulsive disorder. *Eur. Neuropsychopharmacol.* 23, 1423–1431. doi: 10.1016/j.euroneuro.2013.05.012

Denys, D., Van Der Wee, N., Janssen, J., De Geus, F., and Westenberg, H. G. (2004). Low level of dopaminergic D2 receptor binding in obsessive-compulsive disorder. *Biol. Psychiatry* 55, 1041–1045. doi: 10.1016/j.biopsych.2004.01.023

Dong, M. X., Feng, X., Xu, X. M., Hu, L., Liu, Y., Jia, S. Y., et al. (2018a). Integrated analysis reveals altered lipid and glucose metabolism and identifies NOTCH2 as a biomarker for Parkinson’s disease related depression. *Front. Mol. Neurosci.* 11:257. doi: 10.3389/fnmol.2018.00257

Dong, M. X., Hu, L., Huang, Y. J., Xu, X. M., Liu, Y., and Wei, Y. D. (2017a). Cerebrovascular risk factors for patients with cerebral watershed infarction: a case-control study based on computed tomography angiography in a population from Southwest China. *Medicine* 96:e7505. doi: 10.1097/MD.0000000000007505

Dong, M. X., Hu, Q. C., Shen, P., Pan, J. X., Wei, Y. D., Liu, Y. Y., et al. (2016). Recombinant tissue plasminogen activator induces neurological side effects independent on thrombolysis in mechanical animal models of focal cerebral infarction: a systematic review and meta-analysis. *PLoS ONE* 11:e0158848. doi: 10.1371/journal.pone.0158848

Dong, M. X., Li, C. M., Shen, P., Hu, Q. C., Wei, Y. D., Ren, Y. F., et al. (2018b). Recombinant tissue plasminogen activator induces long-term anxiety-like behaviors via the ERK1/2-GAD1-GABA cascade in the hippocampus of a rat model. *Neuropharmacology* 128, 119–131. doi: 10.1016/j.neuropharm.2017.09.039

Dong, M. X., Xu, X. M., Hu, L., Liu, Y., Huang, Y. J., and Wei, Y. D. (2017b). Serum butyrylcholinesterase activity: a biomarker for Parkinson’s disease and related dementia. *Biomed. Res. Int.* 2017:1524107. doi: 10.1155/2017/1524107
Dong et al. (2020) presented their findings on the dopaminergic system in anxiety disorder. They observed significant changes in the dopamine system, particularly in the basal ganglia, which correlated with anxiety symptoms. Their study used a range of imaging techniques, including positron emission tomography (PET) and single-photon emission computed tomography (SPECT), to assess dopamine transporter density and dopamine D2 receptor availability. The results showed lower availability of striatal dopamine transporters in major depression and obsessive-compulsive disorder.

Mohler, H. (2012). The GABA system in anxiety and depression and its therapeutic potential. *Neuropharmacology* 62, 42–53. doi: 10.1016/j.neuropharm.2011.08.040

Nakamura, K., Sekine, Y., Ouchi, Y., Tsuji, M., Yoshikawa, E., Futatsubashi, M., et al. (2010). Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. *Arch. Gen. Psychiatry* 67, 59–68. doi: 10.1001/archgenpsychiatry.2009.137

Nikolaus, S., Antke, C., Beu, M., and Müller, H. W. (2010). Cortical GABA, striatal dopamine and midbrain serotonin as the key players in compulsive and anxiety disorders—from in vivo imaging studies. *Rev. Neurosci.* 21, 119–139. doi: 10.1515/REVNUE.2010.2.1.119

Nikolaus, S., Hautzel, H., and Müller, H. W. (2014). Focus on GABAA receptor function: a comparative analysis of in vivo imaging studies in neuropsychiatric disorders. *Nuclear Medicine* 53, 227–237. doi: 10.3413/Nkmed-0647-14-03

Oliver, J. S., O’Keefe, G., Jones, G. R., Burrows, G. D., Tochon-Danguy, H. J., Ackermann, U., et al. (2009). Dopamine D1 receptor binding in the striatum of patients with obsessive-compulsive disorder. *J. Affect. Disord.* 114, 321–326. doi: 10.1016/j.jad.2008.06.020

Oliver, J. S., O’Keefe, G., Jones, G. R., Burrows, G. D., Tochon-Danguy, H. J., Ackermann, U., et al. (2010). Dopamine D(1) receptor binding in the anterior cingulate cortex of patients with obsessive-compulsive disorder. *Psychiatry Res.* 183, 85–88. doi: 10.1016/j.psychres.2010.04.004

Perani, D., Garibotto, V., Gori, A., Moresco, R. M., Henin, M., Panzacchi, A., et al. (2008). In vivo PET study of SHT(2A) serotonin and D(2) dopamine dysfunction in drug-naive obsessive-compulsive disorder. *Neuroimage* 42, 306–314. doi: 10.1016/j.neuroimage.2008.04.233

Pine, A., Shiner, T., Seymour, B., and Dolan, R. J. (2010). Dopamine, time, and impulsivity in humans. *J. Neurosci.* 30, 8888–8896. doi: 10.1523/JNEUROSCI.6028-09.2010

Plaven-Sigray, P., Hedman, E., Ikonen, P., Matheson, G., Forsberg, A., Djurfeldt, D., et al. (2016). Elevated levels of orbitalfrontal dopamine D2 receptors in patients with social anxiety disorder. *J. Cereb. Blood Flow Metab.* 36, 677–678.

Reinhold, J. A., Rickels, K. (2015). Pharmacological treatment for generalized anxiety disorder in adults: An update. *Expert Opin. Pharmacother.* 16, 1691–1681. 10.1517/14656566.2015.1059424

Schleifer, F. R., Abi-Dargham, A., Martinez, D., Sliestein, M., Hwang, D. R., Liebowitz, M. R., et al. (2009). Dopamine transporters, D2 receptors, and dopamine release in generalized social anxiety disorder. *Depress. Anxiety* 26, 411–418. doi: 10.1002/da.20543

Schleifer, F. R., Liebowitz, M. R., Abi-Dargham, A., Zee-Ponce, Y., Lin, S. H., and Laruelle, M. (2000). Low dopamine D(2) receptor binding potential in social phobia. *Am. J. Psychiatry* 157, 457–459. doi: 10.1176/appi.ajp.157.3.457

Schleifer, F. R., Martinez, D., Abi-Dargham, A., Zee-Ponce, Y., Blair Simpson, H., Liebowitz, M. R., et al. (2008). Striatal dopamine D2 receptor availability in OCD with and without comorbid social anxiety disorder: preliminary findings. *Depress. Anxiety* 25, 1–7. doi: 10.1002/da.20268

Schirg, R. R., Draisma, L. W., Wijnen, J. P., Boks, M. P., Koevoets, M. J., Joëls, M., et al. (2014). Brain GABA levels across psychiatric disorders: a systematic literature review and meta-analysis of 1H-MRS studies. *Hum. Brain Mapp.* 44, 56–59. doi: 10.1002/hbm.23244

Spencer, A. E., Uchida, M., Kenworthy, T., Keary, C. J., and Biederman, J. (2014). Glutamatergic dysregulation in pediatric psychiatric disorders. *Frontiers in Neuroscience* | Volume 14 | Article 608520 | December 2020

Katzman, M. A., Bleau, P., Blier, P., Chokka, P., Kjernisted, K., Van Ameringen, M., et al. (2014). Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry* 14 (Suppl. 1):S1. doi: 10.1186/1471-244X-14-S1-S1

Kessler, R. C., Angermeyer, M., Anthony, J., C. De Graaf, R. O. N., Demyttenaere, K., et al. (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization’s World Mental Health Survey Initiative. *World Psychiatry* 6, 168–176.

Kim, C. H., Koo, M. S., Cheon, K. A., Ryu, Y. H., Lee, J. D., and Lee, H. S. (2003). Dopamine transporter density of basal ganglia assessed with [123I]IPT SPECT in obsessive-compulsive disorder. *Eur. J. Nucl. Med. Mol. Imaging* 30, 1637–1643. doi: 10.1007/s00259-003-1245-7

Lee, I. T., Tsai, H. C., Chi, M. H., Chang, W. H., Chen, K. C., Lee, I. H., et al. (2015). Lower availability of striatal dopamine transporter in generalized anxiety disorder: a preliminary two-ligand SPECT study. *Int. Clin. Psychopharmacol.* 30, 175–178. doi: 10.1097/YIC.0000000000000067

Leggio, G. M., Bucolo, C., Platania, C. B., Salomone, S., and Drago, F. (2016). Current drug treatments targeting dopamine D3 receptor. *Pharmacol. Ther.* 165, 164–177. doi: 10.1016/j.pharmthera.2016.06.007

Li, Z., He, Y., Tang, J., Zong, X., Hu, M., and Chen, X. (2015). Molecular imaging of striatal dopamine transporters in major depression—a meta-analysis. *J. Affect. Disord.* 174, 137–145. doi: 10.1016/j.jad.2014.11.045

Maron, E., Nutt, D. J., Kukka, J., and Tiihonen, J. (2010). Dopamine transporter binding in females with panic disorder may vary with clinical status. *J. Psychiatr. Res.* 44, 56–59. doi: 10.1016/j.jpsychires.2009.04.014

Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G. (2010). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int. J. Surg.* 8, 336–341. doi: 10.1016/j.ijsu.2010.02.007
disorders: a systematic review of the magnetic resonance spectroscopy literature. *J. Clin. Psychiatry* 75, 1226–1241. doi: 10.4088/JCP.13r08767

Steeves, T. D., Ko, J. H., Kideckel, D. M., Rusjan, P., Houle, S., Sandor, P., et al. (2010). Extraprefrontal dopaminergic dysfunction in tourette syndrome. *Ann. Neurol.* 67, 170–181. doi: 10.1002/ana.21809

Stein, D., Koen, N., Fineberg, N., Fontenelle, L., Matsunaga, H., Osser, D., et al. (2012). A 2012 evidence-based algorithm for the pharmacotherapy for obsessive-compulsive disorder. *Curr. Psychiatry Rep.* 14, 211–219. doi: 10.1007/s11920-012-0268-9

Tiihonen, J., Kuikka, J., Bergstrom, K., Lepola, U., Koponen, H., and Leinonen, E. (1997). Dopamine reuptake site densities in patients with social phobia. *Am. J. Psychiatry* 154, 239–242. doi: 10.1176/ajp.154.2.239

Van der Wee, N. J., Stevens, H., Hardeman, J. A., Mandl, R. C., Denys, D. A., Van Megen, H. J., et al. (2004). Enhanced dopamine transporter density in psychotropic-naive patients with obsessive-compulsive disorder shown by $[^{123}]$I–β-CIT SPECT. *Am. J. Psychiatry* 161, 2201–2206. doi: 10.1176/appi.ajp.161.12.2201

Van der Wee, N. J., Van Veen, J. F., Stevens, H., Van Vliet, I. M., Van Rijk, P. P., and Westenberg, H. G. (2008). Increased serotonin and dopamine transporter binding in psychotropic medication-Naive patients with generalized social anxiety disorder shown by $^{123}$I–β-(4-iodophenyl)-tropane SPECT. *J. Nucl. Med.* 49, 757–763. doi: 10.2967/jnumed.107.045518

Wooten, D., Goer, F., Beltzer, M., Vitaliano, G., Brennan, B., Crowley, D., et al. (2013). Reduced striatal dopamine transporter binding in major depressive disorder. *J. Nucl. Med.* 56.

Yatham, L. N., Liddle, P. F., Shah, I. S., Lam, R. W., Ngan, E., Scarrow, G., et al. (2002). PET study of $^{18}$F-$6$-fluoro-$L$-dopa uptake in neuroleptic and mood-stabilizer-naive first-episode nonpsychotic mania: effects of treatment with divalproex sodium. *Am. J. Psychiatry* 159, 768–774. doi: 10.1176/appi.ajp.159.5.768

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Copyright © 2020 Dong, Chen and Hu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.**