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Reduced Striatal Dopamine Transmission as a Transdiagnostic Mechanism for Psychomotor Retardation

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Research Background and Motivation

The general concept underlying this research project is the close connection between mental state and physical movement. For instance, neurological movement disorders such as Huntington's disease and Parkinson's disease exhibit prominent psychiatric symptoms, while psychiatric disorders like depression and schizophrenia frequently manifest with abnormal movements. A pattern of reduced striatal dopamine transmission across these conditions was noted across these disorders by my supervisor Dr Jonathan Rogers, which led to the conceptualisation of this research.

Though slightly different in nature, my interest in the interconnection between physical movement and mental state came from a personal revelation: the reciprocal influence between my mental state and dance. From the scientific literature on movement therapy and its positive impact on psychological well-being, I came across the potential of a bi-directional link, where mental states could shape movement and movement, in turn, could influence mental well-being.

Research Focus and Implications

Within the broad topic of the neuropsychiatry of movement, this research project focused on the relationship between striatal dopamine transmission and psychomotor symptoms of various psychiatric and neurological conditions. Out of several neurotransmitters, dopamine was of particular interest given its central role in the basal ganglia motor loop, particularly the nigrostriatal pathway (connecting the substantia nigra pars compacta to the caudate and putamen of the dorsal striatum). The degeneration of dopaminergic neurons in the substantia nigra pars compacta is one of the primary pathophysiological features of conditions such as Parkinson's disease,[1] associated with cardinal symptoms such as hypokinesia, bradykinesia and rigidity. These symptoms fall under the definition of psychomotor retardation: "a visible generalised slowing of movements and speech" as defined by the ICD-11.[2] However, we also acknowledged that there are other definitions that consider movement initiation, amount and velocity; and make reference to the cognitive aspects of PMR.[3–5]

Previous research has indicated that both neurological and psychiatric causes of psychomotor retardation share common features, particularly pointing to disruptions in dopaminergic transmission.[6,7] Thus, we investigated the hypothesis that reduced striatal dopamine is a transdiagnostic mechanism for PMR, discussing a range of disorders including: Parkinson's disease, Parkinson's plus syndromes such as multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy and dementia with Lewy bodies; drug-induced parkinsonism, neuroleptic malignant syndrome, catatonia, depression and obsessional slowness; while also considering hyperkinetic movement disorders, which clinically appear as the opposite of psychomotor retardation.[8]

By focusing on striatal dopamine, one of our aims was to increase the anatomically and mechanistically specific we could be in describing its transmission, in terms of synaptic location (pre/post), component (nerve terminal/transporter/receptor) and function (storage/reuptake/binding). Identifying a shared pathophysiology among conditions may have clinical implications for more personalised treatments. Moreover, 50-60% of depressed patients do not respond adequately to antidepressants,[9] highlighting the pressing need for novel therapeutic interventions. A more comprehensive understanding of the role of the dopamine system may also have significant implications for repurposing dopaminergic drug treatments for these neuropsychiatric conditions.

Methodology

A narrative review approach was used to investigate the hypothesis that reduced striatal dopamine transmission is a common transdiagnostic mechanism across neurological and psychiatric disorders. The paper comprised of an abstract, introduction, a review of findings from six major areas: clinical features, laboratory markers, molecular neuroimaging, epidemiology and treatment responses to dopaminergic medication and electroconvulsive therapy (ECT) respectively, and a discussion to evaluate whether there is corroborating evidence to support the hypothesis. My focus was on reviewing the evidence from clinical features and neuroimaging, and the creation of the striatal dopaminergic synapse illustration. I also contributed to writing the discussion and synthesising it with the work of my collaborators to make the section coherent.

Two main electronic sources (Google Scholar, PubMed/Medline) were searched to identify relevant manuscripts published up to July 2024. Our initial search was done according to each condition (Parkinson's disease, Parkinson's plus syndromes, drug-induced parkinsonism, neuroleptic malignant syndrome, catatonia, psychomotor retardation in depression, obsessional slowness, hyperkinetic disorders) in combination with the keywords "dopamin*", "psychomotor speed" and/or "psychomotor retardation". The reference lists of the manuscripts were examined for relevant and additional evidence. Only articles with available full texts or sufficiently detailed abstracts written in English were included.

Reflections

This six-week research project was completed under the supervision of Dr Jonathan Rogers. The end-product, although still in progress, will hopefully lead to the publication of my first research paper.

At first, I found it overwhelming to locate and synthesise the literature, which highlighted the need to develop a system tailored to my way of working. My initial approach, particularly while researching clinical

features, lacked structure, making it difficult to keep track of what I had read. This motivated me to develop a more systematic way of recording information using citation software. This experience also taught me the importance of organising time independently and coordinating effectively with collaborators. We were each responsible for different sections, and it became clear that good communication and clarity were essential for ensuring our work linked cohesively.

Through this project, I engaged deeply with the literature, enhancing my understanding of research methods, academic writing, and communication. I developed my analytical skills by evaluating study quality, identifying trends, gaps, and contradictions in the literature, and drawing evidence-based conclusions. The process of writing a paper, including scientific illustration, has been a valuable learning experience, emphasising the importance of methodological rigor and comprehensive literature exploration. Giving oral presentations on our findings allowed me to practice summarising and articulating research in an engaging manner, and I learned the importance of being proactive in asking questions to clarify and deepen my understanding.

Throughout the process, there was also the valuable opportunity of receiving feedback from other leading researchers in the field as co-authors of our paper. Their insights helped me to see my work from different perspectives. Engaging with experienced researchers also highlighted the importance of staying open to constructive criticism and continuously striving for excellence in academic work. This interaction not only enhanced my confidence but also underscored the collaborative nature of research, where the exchange of ideas and perspectives is crucial to advancing knowledge in the field.

Overall, my six-week research project was an insightful and challenging experience. Beyond the valuable insights gained from my own research (detailed in the following extracts from the manuscript), the entire process offered a profound immersion into a new environment. I am immensely grateful for this opportunity and the meaningful connections I have built along the way. This experience has equipped me with a range of transferable skills and opened my eyes to a career path in research.

Manuscript Extracts

Target journal: Brain – Journal of Neuroscience Research

Clinical Features

Reduced dopaminergic transmission in the dorsal striatum leads to the cardinal motor symptoms of Parkinson's disease, such as bradykinesia (slowness in spontaneous movement) and rigidity,[10] although its contribution in tremor has been contested.[11] Evidence shows bradyphrenia (slowness in cognitive processing[12]) and bradykinesia often co-occur in Parkinson's disease,[13,14] with slowed speech characteristic of PMR being a potential manifestation of bradyphrenia.[8,15] However, some observations note abnormally rapid speech in Parkinson's disease patients,[16] though recent studies investigating speech rate report mixed findings.[17–20] While some studies disputed the presence of bradyphrenia in Parkinson's disease,[21,22] others predominantly supported a significant correlation between motor and cognitive slowing in Parkinson's disease.[23] Specifically, bradykinesia severity correlates with compromised psychomotor speed,[24] and extent of cognitive impairment.[25] Since nigrostriatal dopaminergic deficiency is a putative pathophysiological cause of motor impairment in Parkinson's disease, it likely also underlies its cognitive clinical features.

Other neurological disorders present clinical features comparable to Parkinson's disease. Various Parkinson's plus syndromes such as multiple system atrophy and progressive supranuclear palsy present parkinsonism (rigidity, bradykinesia, tremor), with corticobasal degeneration also displaying freezing of gait.[26] In neuroleptic malignant syndrome, patients exhibit akinesia, cogwheel rigidity and compromised internal initiation of movements.[27] drug-induced parkinsonism includes rigidity, bradykinesia, unstable gait, and impaired movement control.[28,29] Bradykinesia also occurs in hyperkinetic disorders such as dystonia, chorea, and essential tremor.[30] These are characterised by excessive, uncontrollable movements and a presumed hyperdopaminergia; contrasting the slowness and hypodopaminergia of hypokinetic disorders such as parkinsonism.[31,32] Catatonia shares motor symptoms with Parkinson's disease (see *Table 1* for comparison), such as akinesia, though its rigidity differs from the cogwheel rigidity of Parkinson's disease.[27] Additionally, motor blocking (*Sperrung*) in catatonia and freezing of gait in Parkinson's disease both present as sudden motor disabilities, characterised respectively by an abrupt cessation in voluntary movement or speech and an unwanted inability to move.[33,34]

Excited catatonia, characterised by agitation, differs markedly from the retardation of akinetic catatonia.[35] While this suggests reduced dopaminergic transmission may not fully explain its clinical presentation, catatonia may be considered a heterogeneous syndrome with subtypes that have varying dopaminergic pathology. The comorbidity of disorders associated with opposite dopaminergic imbalances, such as psychosis with catatonia or Parkinson's disease,[36,37] adds further complexity. However, Friedhoff's restitutive hypothesis[38] suggests that restorative mechanisms could partially account for catatonia's heterogeneity and the contradictory apparent paradoxes of comorbid psychosis.

Overlaps in motor, cognitive and affective clinical features are also observed across psychiatric and neurological disorders. obsessional slowness shares clinical features such as posturing, slowed movement, difficulty initiating voluntary action and echolalia with catatonia[39]; while the muscular rigidity, reduced facial expression and delayed initiation of spontaneous movement resembles Parkinson's disease,[40] suggesting shared neural disruptions.[41] Researchers have noted a relationship between PMR in depression and bradykinesia in Parkinson's disease,[42–44] observing comparable clinical presentations of a slow, shuffling gait, hunched posture, expressionless and static masked facies, and a decrease in both the speed and volume of speech;[45] others have identified different patterns of motor impairment.[28] Relatedly, PMR in depression is associated with bradyphrenia in Parkinson's disease.[6,46] Hence, a common dopaminergic mechanism likely underlies motor and cognitive slowness in Parkinson's disease and depression. However, the potential confounding effects of aging should be acknowledged, as it relates to a 15% decrease in psychomotor and cognitive performance and dopaminergic neuron loss in the substantia nigra pars compacta to akin to Parkinson's disease, albeit more moderate.[47,48]

Within depression, PMR accounts for a significant proportion (60%) of the variance in Depressive Retardation Rating Scale scores,[49] and correlates with anhedonia, a core symptom of depression characterised by the diminished ability to experience pleasure.[50] Similarly, PMR is correlated with anhedonia in Parkinson's disease,[51] and the presence of bradykinesia and rigidity.[52] Despite some contesting evidence,[53,54] it seems plausible for anhedonia to be a common consequence of hypodopaminergic states rather than an independent entity. This is supported by how anhedonia is traditionally attributed to mesolimbic dopaminergic deficiency,[55] and the speculation that nigrostriatal dopaminergic projections may also underlie anhedonic responses.[56]

In summary, similarities in clinical features indicate striatal dopamine as a plausible common substrate for PMR across neurological and psychiatric conditions.

Table 1: Comparison of Shared Clinical Features between Parkinson's disease and Catatonia

	Parkinson's disease[57–60]	**Catatonia**[36,59,61–63]
Motor		
Rigidity	Present (muscular hypertonus), especially cogwheel rigidity	Often present, but tone may also be normal or reduced. Waxy flexibility is highly specific.
Hypokinesia (slowed or absence of movement)	Bradykinesia, akinesia	Stupor (decreased psychomotor movement and reactivity), akinesia
Tremor	Present at rest and postural	Not typically observed
Facial manifestations	Masked facies, reduced blink rates	Flat affect, staring and reduced blink rates
Sudden motor freezing	Freezing of gait (sudden, unwanted inability to move)	Motor blocking (*Sperrung;* abrupt cessation in voluntary movement or speech)
Non-motor		
Altered mental status	Depression, apathy, anhedonia, anxiety, psychosis	Depression, mania, anxiety, psychosis

Neuroimaging

PET and single photon emission computed tomography (SPECT) enable the quantification of dopaminergic transmission in the brain (see *Figure 1* for a schematic representation of dopaminergic transmission and imaging radioligand action sites).

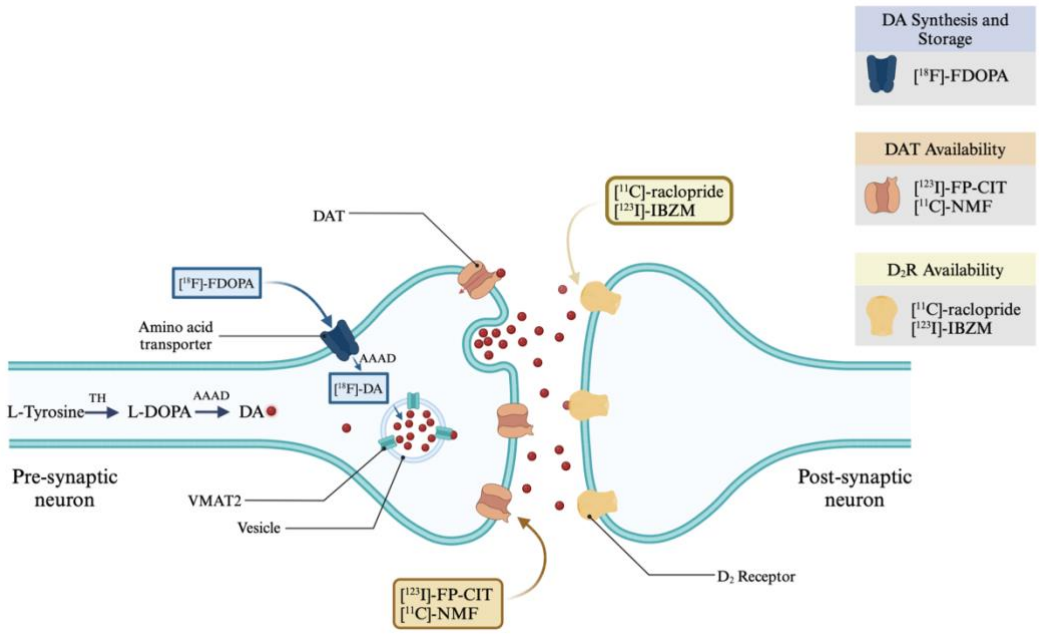

Figure 1: Simplified representation of the dopamine synthetic pathway and radioligand action sites in a striatal dopaminergic synapse.

In the final two steps of the dopamine (DA) synthetic pathway, tyrosine hydroxylase (TH) converts tyrosine to L-DOPA, which is subsequently converted into DA by aromatic L-amino acid decarboxylase (AAAD). DA is stored in vesicles for tonic and phasic release. The diffusion of DA across the synaptic cleft to and its binding to post-synaptic DA D_2 receptors initiates intracellular cascades in the post-synaptic neuron that enables signal transmission. Following release, dopamine transporters (DAT) facilitate the reuptake of DA into the pre-synaptic neuron, which is then transported back into the vesicle by vesicular monoamine transporter type 2 (VMAT2).

Selected PET/SPECT radioligands and their site of action are depicted: [^{18}F]-FDOPA is taken up into the pre-synaptic dopaminergic neuron via an amino acid transporter, then decarboxylated by AAAD into flurodopamine ([^{18}F]-DA) and temporarily stored in vesicles. Thus, [^{18}F]-FDOPA uptake can be interpreted as an indication of pre-synaptic DA synthesis and storage capacity; [^{11}C]-NMF uptake and [^{123}I]-FP-CIT binding indicate the reuptake capacity of DAT; [^{11}C]-raclopride and [^{123}I]-IBZM binding indicate post-synaptic D_2 receptor availability. Due to their competition with endogenous DA for binding, these radioligands can additionally derive an estimate of DA release by comparing ligand binding before and after a dopamine-stimulating event.

DA — dopamine. TH — tyrosine hydroxylase. L-DOPA — L-3,4-dihydroxyphenylalanine/Levodopa. AAAD – aromatic L-amino acid decarboxylase. DAT — dopamine transporters. VMAT2 — Vesicular monoamine transporter type 2. [^{18}F]-FDOPA — 6-[18F]Fluoro-L-3,4-dihydroxyphenylalanine. [^{18}F]-DA — flurodopamine. [^{11}C]-NMF — S-^{11}C-nomifensine. [^{123}I]-FP-CIT — N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane/^{123}I-Ioflupane. [^{123}I]-IBZM — Iodine-123-Iodobenzamide.

In Parkinson's disease, significant reductions in striatal [^{18}F]-FDOPA uptake and putaminal [^{11}C]-NMF binding correlate with the severity and lateralisation of motor retardation, specifically bradykinesia and rigidity.[64–67] [^{123}I]-FP-CIT SPECT studies show an asymmetrical decline in striatal dopamine transporter (DAT) binding following a rostro-caudal gradient with increased duration and severity of Parkinson's disease.[68,69] Notably, tremor does not correlate with [^{18}F]-FDOPA uptake,[67,70] striatal DAT binding,[68,71] nor other clinical features. This dissociation, coupled with the typical absence of tremor in catatonia and PMR in depression, supports a specific relationship between reduced striatal dopamine transmission and PMR.

In early Parkinson's disease, initial upregulation of striatal post-synaptic D_2 receptors (D_2R) shown by [^{11}C]-raclopride-PET and [^{123}I]-IBZM-SPECT has been interpreted as a compensatory mechanism for pre-synaptic dopaminergic nerve terminal loss, followed by downregulation more prominent in the caudate

approximately four years following motor symptom onset.[72] Though it remains difficult to ascertain whether downregulation results from disease progression or medication,[73] consistent observations of higher striatal D_2R binding contralateral to predominant motor symptoms suggest that the initial upregulation is a temporary compensatory response to dopamine depletion resulting from pre-synaptic degeneration in early Parkinson's disease.[72] This is in accord with the inverse correlation observed between [^{18}F]-FDOPA uptake and [^{11}C]-raclopride binding in L-DOPA naïve Parkinson's disease patients.[74]

Non-motor symptoms of Parkinson's disease also correlate with dopaminergic deficits. Reduced dorsal striatal DAT binding is associated with anhedonia,[75] and caudate pre-synaptic dopaminergic nerve terminal and transporter dysfunction correlates with slower cognitive speed and impaired verbal fluency.[76,77] These results suggest that compromised nigrostriatal pre-synaptic dopamine storage and reuptake capacity contribute to endogenous dopamine depletion affecting motor and non-motor symptoms in Parkinson's disease, as reflected by post-synaptic D_2R density changes.

Similarly, motor symptoms of multiple system atrophy and progressive supranuclear palsy relate to reduced striatal [^{18}F]-FDOPA uptake and D_2R density, and CBD shows asymmetric decreases in caudate and putaminal uptake.[78] In drug-induced parkinsonism, decreased [^{123}I]-FP-CIT binding predicts levodopa response and parkinsonian symptom progression,[79] with reduced putaminal [^{18}F]-FDOPA uptake observed in cases of continued or deteriorating parkinsonism post-withdrawal.[80] This suggests that drug-induced parkinsonism likely occurs in an at-risk population with subclinical pre-synaptic nigrostriatal dysfunctions.[81] In neuroleptic malignant syndrome, [^{123}I]-IBZM-SPECT reveals near-absent basal ganglia D_2R binding in the acute phase and persistent mild parkinsonian symptoms despite near-normal D_2R availability after four months,[82] indicating high post-synaptic D_2R occupancy as a mechanism for reduced dopaminergic transmission associated with motor impairments.

Studies on catatonia mainly concentrate on pre-synaptic function, with limited data concerning post-synaptic D_2Rs.[83] [^{18}F]-FDOPA-PET studies found decreased putaminal and caudate uptake in patients with catatonic schizophrenia relative to other patients with schizophrenia and healthy controls,[84–86] and comparable caudate Ki values to PD,[87] suggesting a similar intracellular hypodopaminergia. However, since these studies included few catatonic patients and did not specify their clinical state during scans, observations may be state-specific. [^{123}I]-FP-CIT-SPECT evaluations demonstrate a correlation between striatal DAT density changes and progression of catatonic symptoms, observing a restoration of initially reduced striatal DAT-SPECT accumulation post-treatment with ECT or benzodiazepines.[88] Although benzodiazepines, a first line treatment for catatonia, may reduce the amplitude of phasic dopamine release via $GABA_A$ receptor activation,[89–91] their net effect on dopaminergic transmission remains unclear, making it difficult to define a relationship with the observed restoration. Nevertheless, the reversible DAT dysfunction indicates that striatal dopaminergic transmission partially underlies catatonia.

In depression, striatal [^{123}I]-IBZM binding in PMR patients initially increases pre-treatment and subsequently decreases post-treatment relative to healthy controls and non-PMR patients.[92] Concordantly,

increased right striatal [^{123}I]-IBZM binding correlates positively with movement time and negatively with verbal fluency.[93] Moreover, depressed patients with motor retardation showed significantly higher putaminal [^{11}C]-raclopride binding correlated with motor speed,[94] and PMR patients presented lower left caudate [^{18}F]-FDOPA uptake.[95] These findings suggest that both impaired dopamine storage in pre-synaptic nerve terminals and reduced striatal post-synaptic D_2R availability associate with PMR in depression.

However, patients with obsessional slowness exhibit normal striatal [^{18}F]-FDOPA uptake, with no evidence suggesting that their extreme slowness relates to nigrostriatal pre-synaptic dysfunction.[96] Evidence in hyperkinetic disorders is varied, mostly showing normal or increased striatal DAT binding in essential tremor and tic disorders.[97] In dystonia, decreased striatal D_2R binding potential but normal [^{123}I]-FP-CIT binding and [^{18}F]-FDOPA uptake imply a dopaminergic transmission disturbance from reduced post-synaptic receptor availability rather than pre-synaptic irregularities.[97–99]

Overall, neuroimaging evidence predominantly support associations between reduced striatal dopaminergic transmission and psychomotor deficits across conditions (see *Table 2* for summary), more pronounced in the dorsal than ventral striatum. Post-synaptic dysfunctions primarily involve D_2Rs, but this may result from less extensive investigations on D_1Rs, especially in conditions other than Parkinson's disease. However, available PET studies examining Parkinson's disease patients typically observe no differences in striatal D_1R binding compared to healthy controls.[100] For Parkinson's disease, Parkinson's plus syndromes and PMR in depression, there seems to be sufficient evidence to specify subregional dopaminergic differences between the putamen and caudate, and differentiate dysfunctions by synaptic region, compartment and function. However, evidence for drug-induced parkinsonism, neuroleptic malignant syndrome, catatonia, obsessional slowness and hyperkinetic disorders is less comprehensive and requires further research.

Table 2: Summary of Imaging Findings by Synaptic Region

Condition	Pre-synaptic Findings		Post-synaptic findings	
	Tracer	Interpretation	Tracer	Interpretation
Parkinson's disease	↓ Striatal [^{18}F]-FDOPA uptake [64–67] ↓ Putaminal [^{11}C]-NMF binding [64,66] Asymmetrical ↓ striatal [^{123}I]-FP-CIT binding following a rostro-caudal gradient[101]	Reflective pre-synaptic DA synthesis, storage and reuptake dysfunction more prominent in the putamen Suggestive of alternative pathophysiology, supportive of specific relationship between ↓ DA transmission and PMR	Initial ↑ [^{123}I]-IBZM and [^{11}C]-raclopride binding in striatum contralateral to predominant motor symptoms, subsequent ↓ caudate binding four years after onset [72]	Initial ↑ may be compensatory mechanism for pre-synaptic DA nerve terminal loss Though ↓ D_2R availability may not directly cause motor symptoms, D_2R density changes may be driven by endogenous DA depletion resulting from pre-synaptic impairments
Parkinson's plus syndromes	MSA, PSP: ↓ Striatal [^{18}F]-FDOPA uptake [78] CBD: Asymmetrical ↓ in caudate and putaminal [^{18}F]-FDOPA uptake		MSA, PSP: ↓ striatal [^{11}C]-raclopride binding relative to PD and healthy controls	Indicative of ↓ striatal D_2R density
Drug-Induced Parkinsonism	↓ [^{123}I]-FP-CIT binding[79] ↓ putaminal [^{18}F]-FDOPA uptake[80]	DIP likely occurs in an at-risk population with subclinical pre-synaptic nigrostriatal dysfunctions in DA storage and reuptake [81]	↓ putaminal [^{11}C]-raclopride binding[102]	Indicative of ↑ D_2R blockade possibly associated with extrapyramidal symptoms
Neuroleptic Malignant Syndrome	To the author's knowledge, no studies to date has examined this		Near absent basal ganglia [^{123}I]-IBZM binding in acute phase → near-normal binding despite persistent mild parkinsonian symptoms after four months [82]	Suggests high post-synaptic D_2R occupancy may be a mechanism for reduced DA transmission associated with motor impairments
Catatonia	↓ putaminal [84,85] and caudate[86] [^{18}F]-FDOPA uptake Initial ↓ [^{123}I]-FP-CIT binding → Restored binding post-ECT/benzodiazepine treatment[88]	Reversible DAT dysfunction indicates striatal DA transmission partially underlies catatonia	To the author's knowledge, no studies to date has examined this	
Obsessional Slowness	Normal striatal [^{18}F]-FDOPA uptake [96]	Insufficient evidence to suggest association between extreme slowness and impaired DA synthesis and storage	To the author's knowledge, no studies to date has examined this	
Psychomotor Retardation in Depression	↓ left caudate [^{18}F]-FDOPA uptake in PMR patients relative to healthy controls and non-PMR patients [95]	DA hypofunction in left caudate may be associated with PMR in depression	Initial ↑ striatal [^{123}I]-IBZM binding pre-treatment, subsequent ↓ post-treatment in PMR patients relative to healthy controls and non-PMR patients [92] ↑ right striatal [^{123}I]-IBZM binding [95] ↑ putaminal [^{11}C]-raclopride binding [94]	Initial ↑ pre-treatment may suggest compensatory D_2R upregulation and/or decreased synaptic dopamine, subsequent ↓ post-treatment may indicate normalisation of D_2R availability or response to treatment Higher striatal D_2R availability may indirectly indicate endogenous DA depletion associated with motor and cognitive impairments

Summary of Findings (including excerpts from Discussion)

There is some compelling evidence supporting striatal dopamine as a transdiagnostic mechanism for PMR. The overlapping clinical features across conditions imply striatal dopamine as a common substrate associated with PMR. Epidemiological evidence indicates that transdiagnostic PMR in clinical populations may result from predisposed dopaminergic dysfunction or antipsychotic effects. Molecular neuroimaging and laboratory evidence mainly associate reduced striatal transmission with PMR, though evidence for hyperkinetic disorders does not seem to support the converse hypothesis. Dopaminergic medication appears effective in various conditions with PMR, though inconsistencies exist. Available findings highlight the critical role of striatal dopamine in ECT's therapeutic function, though other mechanisms may be involved. More evidence supports this mechanism for psychomotor complications in Parkinson's disease, Parkinson's plus syndromes and PMR in depression, whereas evidence for other disorders is less compelling.

The evidence examined in this narrative review generally support reduced dorsal striatal dopamine transmission as a transdiagnostic mechanism for PMR across various neurological and psychiatric conditions. That is, reduced transmission could contribute to the pathophysiology of PMR, though it may not be the primary cause. While current evidence is insufficient to conclusively define anatomical and mechanistic specificities, we speculate that dorsal striatal pre-synaptic dysfunctions in dopamine storage and reuptake affects downstream neurotransmission. This could lead to insufficient levels of synaptic dopamine, reflected as changes in post-synaptic D_2R availability. Striatal dopamine should be considered alongside other interacting neurotransmitters, with further investigation needed into medication action sites and the anatomical and mechanistic specifics of striatal transmission.

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References

1. Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet Lond Engl*. 2009;373(9680):2055-2066. doi:10.1016/S0140-6736(09)60492-X

2. World Health Organization (WHO). MB23.N Psychomotor Retardation. In: *International Classification of Diseases, Eleventh Revision (ICD-11)*. ; 2019.

3. Walther S, Alexaki D, Weiss F, et al. Psychomotor Slowing in Psychosis and Inhibitory Repetitive Transcranial Magnetic Stimulation. *JAMA Psychiatry*. 2024;81(6):563-571. doi:10.1001/jamapsychiatry.2024.0026

4. Osborne KJ, Walther S, Shankman SA, Mittal VA. Psychomotor slowing in Schizophrenia: Implications for endophenotype and biomarker development. *Biomark Neuropsychiatry*. 2020;2:100016. doi:10.1016/j.bionps.2020.100016

5. Morrens M, Hulstijn W, Sabbe B. Psychomotor Slowing in Schizophrenia. *Schizophr Bull*. 2007;33(4):1038-1053. doi:10.1093/schbul/sbl051

6. ROGERS D, LEES AJ, SMITH E, TRIMBLE M, STERN GM. BRADYPHRENIA IN PARKINSON'S DISEASE AND PSYCHOMOTOR RETARDATION IN DEPRESSIVE ILLNESS: AN EXPERIMENTAL STUDY. *Brain*. 1987;110(3):761-776. doi:10.1093/brain/110.3.761

7. Hinkle JT, Pontone GM. Reconceptualizing Catatonia as "Psychiatric Parkinsonism." *Am J Geriatr Psychiatry*. 2023;31(12):1206-1208. doi:10.1016/j.jagp.2023.07.010

8. Gurd JM, Bessell N, Watson I, Coleman J. Motor speech versus digit control in Parkinson's disease: A cognitive neuropsychology investigation. *Clin Linguist Phon*. 1998;12(5):357-378. doi:10.1080/02699209808985231

9. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. 2003;53(8):649-659. doi:10.1016/S0006-3223(03)00231-2

10. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci*. 1990;13(7):281-285. doi:10.1016/0166-2236(90)90110-V

11. Grafton ST. Contributions of functional imaging to understanding parkinsonian symptoms. *Curr Opin Neurobiol*. 2004;14(6):715-719. doi:10.1016/j.conb.2004.10.010

12. Brown RG. Disorders of Intention in Parkinsonian Syndromes. In: Bédard MA, Agid Y, Chouinard S, Fahn S, Korczyn AD, Lespérance P, eds. *Mental and Behavioral Dysfunction in Movement Disorders*. Humana Press; 2003:101-112. doi:10.1007/978-1-59259-326-2_7

13. Hsieh YH, Chen KJ, Wang CC, Lai CL. Cognitive and Motor Components of Response Speed in the Stroop Test in Parkinson's Disease Patients. *Kaohsiung J Med Sci*. 2008;24(4):197-203. doi:10.1016/S1607-551X(08)70117-7

14. Muslimović D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*. 2005;65(8):1239-1245. doi:10.1212/01.wnl.0000180516.69442.95

15. Flint AJ, Black SE, Campbell-Taylor I, Gailey GF, Levinton C. Abnormal speech articulation, psychomotor retardation, and subcortical dysfunction in major depression. *J Psychiatr Res*. 1993;27(3):309-319. doi:10.1016/0022-3956(93)90041-Y

16. Canter GJ. Speech Characteristics of Patients with Parkinson's Disease: I. Intensity, Pitch, and Duration. *J Speech Hear Disord*. 1963;28(3):221-229. doi:10.1044/jshd.2803.221

17. Skodda S, Schlegel U. Speech rate and rhythm in Parkinson's disease. *Mov Disord*. 2008;23(7):985-992. doi:10.1002/mds.21996

18. Martínez-Sánchez F, Meilán JJG, Carro J, et al. Speech rate in Parkinson's disease: A controlled study. *Neurol Engl Ed*. 2016;31(7):466-472. doi:10.1016/j.nrleng.2014.12.014

19. Ludlow CL, Connor NP, Bassich CJ. Speech timing in Parkinson's and Huntington's disease. *Brain Lang*. 1987;32(2):195-214. doi:10.1016/0093-934X(87)90124-6

20. Skodda S. Aspects of speech rate and regularity in Parkinson's disease. *J Neurol Sci*. 2011;310(1):231-236. doi:10.1016/j.jns.2011.07.020

21. Duncombe ME, Bradshaw JL, Iansek R, Phillips JG. Parkinsonian patients without dementia or depression do not suffer from bradyphrenia as indexed by performance in mental rotation tasks with and without advance information. *Neuropsychologia*. 1994;32(11):1383-1396. doi:10.1016/0028-3932(94)00071-9

22. Helscher RJ, Pinter MM. Speed and power of higher cerebral functions in parkinsonian patients. *J Neural Transm - Park Dis Dement Sect*. 1993;5(1):35-44. doi:10.1007/BF02260913

23. Sawamoto N, Honda M, Hanakawa T, Fukuyama H, Shibasaki H. Cognitive Slowing in Parkinson's Disease: A Behavioral Evaluation Independent of Motor Slowing. *J Neurosci*. 2002;22(12):5198-5203. doi:10.1523/JNEUROSCI.22-12-05198.2002

24. Mortimer JA, Pirozzolo FJ, Hansch EC, Webster DD. Relationship of motor symptoms to intellectual deficits in Parkinson disease. *Neurology*. 1982;32(2):133-133. doi:10.1212/WNL.32.2.133

25. Huber SJ, Paulson GW, Shuttleworth EC. Relationship of motor symptoms, intellectual impairment, and depression in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1988;51(6):855-858. doi:10.1136/jnnp.51.6.855

26. Deutschländer AB, Ross OA, Dickson DW, Wszolek ZK. Atypical parkinsonian syndromes: a general neurologist's perspective. *Eur J Neurol*. 2018;25(1):41-58. doi:10.1111/ene.13412

27. Northoff G. Catatonia and neuroleptic malignant syndrome: psychopathology and pathophysiology. *J Neural Transm*. 2002;109(12):1453-1467. doi:10.1007/s00702-002-0762-z

28. FLEMINGER S. CONTROL OF SIMULTANEOUS MOVEMENTS DISTINGUISHES DEPRESSIVE MOTOR RETARDATION FROM PARKINSON'S DISEASE AND NEUROLEPTIC PARKINSONISM. *Brain*. 1992;115(5):1459-1480. doi:10.1093/brain/115.5.1459

29. Susatia F, Fernandez HH. Drug-induced parkinsonism. *Curr Treat Options Neurol*. 2009;11(3):162-169. doi:10.1007/s11940-009-0019-3

30. Paparella G, Fasano A, Hallett M, Berardelli A, Bologna M. Emerging concepts on bradykinesia in non-parkinsonian conditions. *Eur J Neurol*. 2021;28(7):2403-2422. doi:10.1111/ene.14851

31. Jankovic J. Treatment of hyperkinetic movement disorders. *Lancet Neurol*. 2009;8(9):844-856. doi:10.1016/S1474-4422(09)70183-8

32. Jankovic J. Dopamine depleters in the treatment of hyperkinetic movement disorders. *Expert Opin Pharmacother*. 2016;17(18):2461-2470. doi:10.1080/14656566.2016.1258063

33. Hoenig J, Toakley JG. The Diagnosis of Stupor. *Psychiatr Neurol (Basel)*. 2008;137(2-3):128-144. doi:10.1159/000134234

34. Lewis SJG, Barker RA. A pathophysiological model of freezing of gait in Parkinson's disease. *Parkinsonism Relat Disord*. 2009;15(5):333-338. doi:10.1016/j.parkreldis.2008.08.006

35. Edinoff AN, Kaufman SE, Hollier JW, et al. Catatonia: Clinical Overview of the Diagnosis, Treatment, and Clinical Challenges. *Neurol Int*. 2021;13(4):570-586. doi:10.3390/neurolint13040057

36. Rosebush PI, Mazurek MF. Catatonia and Its Treatment. *Schizophr Bull*. 2010;36(2):239-242. doi:10.1093/schbul/sbp141

37. Marsh L. Psychosis in Parkinson's Disease. *Curr Treat Options Neurol*. 2004;6:181-189. doi:10.1007/s11940-004-0010-y

38. Friedhoff AJ. A Dopamine-dependent Restitutive System for the Maintenance of Mental Normalcy. *Ann N Y Acad Sci*. 1986;463(1):47-52. doi:10.1111/j.1749-6632.1986.tb21502.x

39. Ganos C, Kassavetis P, Cerdan M, et al. Revisiting the Syndrome of "Obsessional Slowness." *Mov Disord Clin Pract*. 2015;2(2):163-169. doi:10.1002/mdc3.12140

40. HYMAS N, LEES A, BOLTON D, EPPS K, HEAD D. THE NEUROLOGY OF OBSESSIONAL SLOWNESS. *Brain*. 1991;114(5):2203-2233. doi:10.1093/brain/114.5.2203

41. Lees AJ. The Neurobehavioural Abnormalities in Parkinson's Disease and their Relationship to Psychomotor Retardation and Obsessional Compulsive Disorders. *Behav Neurol*. 1989;2(1):485427. doi:10.3233/BEN-1989-2101

42. Caligiuri MP, Ellwanger J. Motor and cognitive aspects of motor retardation in depression. *J Affect Disord*. 2000;57(1):83-93. doi:10.1016/S0165-0327(99)00068-3

43. Rogers MA, Bradshaw JL, Pantelis C, Phillips JG. Frontostriatal deficits in unipolar major depression. *Brain Res Bull*. 1998;47(4):297-310. doi:10.1016/S0361-9230(98)00126-9

44. Sachdev P, Aniss AM. Slowness of movement in melancholic depression. *Biol Psychiatry*. 1994;35(4):253-262. doi:10.1016/0006-3223(94)91256-4

45. Rogers MA, Bradshaw JL, Phillips JG, et al. Parkinsonian Motor Characteristics in Unipolar Major Depression. *J Clin Exp Neuropsychol*. 2000;22(2):232-244. doi:10.1076/1380-3395(200004)22:2;1-1;FT232

46. STARKSTEIN SE, PREZIOSI TJ, BERTHIER ML, BOLDUC PL, MAYBERG HS, ROBINSON RG. DEPRESSION AND COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE. *Brain*. 1989;112(5):1141-1153. doi:10.1093/brain/112.5.1141

47. Hietanen M, Teräväinen H. Cognitive performance in early Parkinson's disease. *Acta Neurol Scand*. 1986;73(2):151-159. doi:10.1111/j.1600-0404.1986.tb03257.x

48. McGeer PL, McGeer EG, Suzuki JS. Aging and extrapyramidal function. *Arch Neurol*. 1977;34(1):33-35. doi:10.1001/archneur.1977.00500130053010

49. Widlöcher DJ. Psychomotor retardation: Clinical, theoretical, and psychometric aspects. *Psychiatr Clin North Am*. 1983;6(1):27-40.

50. Lemke MR, Puhl P, Koethe N, Winkler T. Psychomotor retardation and anhedonia in depression. *Acta Psychiatr Scand*. 1999;99(4):252-256. doi:10.1111/j.1600-0447.1999.tb07221.x

51. Reichmann H, Brecht MH, Köster J, Kraus PH, Lemke MR. Pramipexole in Routine Clinical Practice. *CNS Drugs*. 2003;17(13):965-973. doi:10.2165/00023210-200317130-00003

52. Lemke MR, Brecht HM, Koester J, Kraus PH, Reichmann H. Anhedonia, Depression, and Motor Functioning in Parkinson's Disease During Treatment With Pramipexole. *J Neuropsychiatry Clin Neurosci*. 2005;17(2):214-220. doi:10.1176/jnp.17.2.214

53. Isella V, Iurlaro S, Piolti R, et al. Physical anhedonia in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2003;74(9):1308-1311. doi:10.1136/jnnp.74.9.1308

54. Santangelo G, Vitale C, Trojano L, et al. Relationship between depression and cognitive dysfunctions in Parkinson's disease without dementia. *J Neurol*. 2009;256(4):632-638. doi:10.1007/s00415-009-0146-5

55. Wang S, Leri F, Rizvi SJ. Anhedonia as a central factor in depression: Neural mechanisms revealed from preclinical to clinical evidence. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;110:110289. doi:10.1016/j.pnpbp.2021.110289

56. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. *Trends Neurosci*. 2012;35(1):68-77. doi:10.1016/j.tins.2011.11.005

57. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*. 2008;79(4):368-376. doi:10.1136/jnnp.2007.131045

58. Schrag A. Psychiatric aspects of Parkinson's disease. *J Neurol*. 2004;251(7):795-804. doi:10.1007/s00415-004-0483-3

59. Bhati MT, Datto CJ, O'Reardon JP. Clinical Manifestations, Diagnosis, and Empirical Treatments for Catatonia. *Psychiatry Edgmont*. 2007;4(3):46-52.

60. Dewey RB. Clinical Features of Parkinson's Disease. In: Adler CH, Ahlskog JE, eds. *Parkinson's Disease and Movement Disorders: Diagnosis and Treatment Guidelines for the Practicing Physician*. Humana Press; 2000:71-84. doi:10.1007/978-1-59259-410-8_4

61. Northoff G. What catatonia can tell us about "top-down modulation": A neuropsychiatric hypothesis. *Behav Brain Sci*. 2002;25(5):555-577. doi:10.1017/S0140525X02000109

62. Takacs R, Rihmer Z. Catatonia in Affective Disorders. *Curr Psychiatry Rev*. 2013;9(2):101-105.

63. Wijemanne S, Jankovic J. Movement disorders in catatonia. *J Neurol Neurosurg Psychiatry*. 2015;86(8):825-832. doi:10.1136/jnnp-2014-309098

64. BROOKS DJ, SALMON EP, MATHIAS CJ, et al. THE RELATIONSHIP BETWEEN LOCOMOTOR DISABILITY, AUTONOMIC DYSFUNCTION, AND THE INTEGRITY OF THE STRIATAL DOPAMINERGIC SYSTEM IN PATIENTS WITH MULTIPLE SYSTEM ATROPHY, PURE AUTONOMIC FAILURE, AND PARKINSON'S DISEASE, STUDIED WITH PET. *Brain*. 1990;113(5):1539-1552. doi:10.1093/brain/113.5.1539

65. Broussolle E, Dentresangle C, Landais P, et al. The relation of putamen and caudate nucleus 18F-Dopa uptake to motor and cognitive performances in Parkinson's disease. *J Neurol Sci*. 1999;166(2):141-151. doi:10.1016/s0022-510x(99)00127-6

66. Leenders KL, Salmon EP, Tyrrell P, et al. The Nigrostriatal Dopaminergic System Assessed In Vivo by Positron Emission Tomography in Healthy Volunteer Subjects and Patients With Parkinson's Disease. *Arch Neurol*. 1990;47(12):1290-1298. doi:10.1001/archneur.1990.00530120034007

67. Vingerhoets FJG, Schulzer M, Calne DB, Snow BJ. Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? *Ann Neurol*. 1997;41(1):58-64. doi:10.1002/ana.410410111

68. Benamer HTS, Patterson J, Grosset DG, et al. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: The [123I]-FP-CIT study group. *Mov Disord*. 2000;15(3):503-510. doi:10.1002/1531-8257(200005)15:3<503::AID-MDS1013>3.0.CO;2-V

69. Rinne JO, Burn DJ, Dphil CJM, Quinn NP, Marsden CD, Brooks DJ. Positron emission tomography studies on the dopaminergic system and striatal opioid binding in the olivopontocerebellar atrophy variant of multiple system atrophy. *Ann Neurol*. 1995;37(5):568-573. doi:10.1002/ana.410370505

70. Otsuka M, Ichiya Y, Kuwabara Y, et al. Differences in the reduced 18F-Dopa uptakes of the caudate and the putamen in Parkinson's disease: correlations with the three main symptoms. *J Neurol Sci*. 1996;136(1):169-173. doi:10.1016/0022-510X(95)00316-T

71. Pirker W. Correlation of dopamine transporter imaging with parkinsonian motor handicap: How close is it? *Mov Disord*. 2003;18(S7):S43-S51. doi:10.1002/mds.10579

72. Kaasinen V, Vahlberg T, Stoessl AJ, Strafella AP, Antonini A. Dopamine Receptors in Parkinson's Disease: A Meta-Analysis of Imaging Studies. *Mov Disord*. 2021;36(8):1781-1791. doi:10.1002/mds.28632

73. Thobois S, Jahanshahi M, Pinto S, Frackowiak R, Limousin-Dowsey P. PET and SPECT functional imaging studies in Parkinsonian syndromes: from the lesion to its consequences. *NeuroImage*. 2004;23(1):1-16. doi:10.1016/j.neuroimage.2004.04.039

74. Sawle GV, Playford ED, Brooks DJ, Quinn N, Frackowiak RSJ. Asymmetrical pre-synaptic and post-synaptic changes in the striatal dopamine projection in dopa naïve parkinsonism: Diagnostic implications of the D2 receptor status. *Brain*. 1993;116(4):853-867. doi:10.1093/brain/116.4.853

75. Costello H, Yamamori Y, Reeves S, Schrag AE, Howard R, Roiser JP. Longitudinal decline in striatal dopamine transporter binding in Parkinson's disease: associations with apathy and anhedonia. *J Neurol Neurosurg Psychiatry*. 2023;94(10):863-870. doi:10.1136/jnnp-2022-330790

76. Polito C, Berti V, Ramat S, et al. Interaction of caudate dopamine depletion and brain metabolic changes with cognitive dysfunction in early Parkinson's disease. *Neurobiol Aging*. 2012;33(1):206.e29-206.e39. doi:10.1016/j.neurobiolaging.2010.09.004

77. Rinne JO, Portin R, Ruottinen H, et al. Cognitive Impairment and the Brain Dopaminergic System in Parkinson Disease: [18F]Fluorodopa Positron Emission Tomographic Study. *Arch Neurol*. 2000;57(4):470-475. doi:10.1001/archneur.57.4.470

78. Niccolini F, Politis M. A systematic review of lessons learned from PET molecular imaging research in atypical parkinsonism. *Eur J Nucl Med Mol Imaging*. 2016;43(12):2244-2254. doi:10.1007/s00259-016-3464-8

79. Tinazzi M, Antonini A, Bovi T, et al. Clinical and [123I]FP-CIT SPET imaging follow-up in patients with drug-induced parkinsonism. *J Neurol*. 2009;256(6):910-915. doi:10.1007/s00415-009-5039-0

80. Burn DJ, Brooks DJ. Nigral dysfunction in drug-induced parkinsonism: An ^{18} F-dopa PET study. *Neurology*. 1993;43(3_part_1):552-552. doi:10.1212/WNL.43.3_Part_1.552

81. Tolosa E, Coelho M, Gallardo M. DAT imaging in drug-induced and psychogenic parkinsonism. *Mov Disord*. 2003;18(S7):S28-S33. doi:10.1002/mds.10575

82. Jauss M, Krack P, Franz M, et al. Imaging of dopamine receptors with [123I]iodobenzamide single-photon emission–computed tomography in neuroleptic malignant syndrome. *Mov Disord*. 1996;11(6):726-728. doi:10.1002/mds.870110621

83. Haroche A, Rogers J, Plaze M, et al. Brain imaging in catatonia: systematic review and directions for future research. *Psychol Med*. 2020;50(10):1585-1597. doi:10.1017/S0033291720001853

84. Hietala J, Syvälahti E, Vuorio K, et al. Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. *Lancet Lond Engl*. 1995;346(8983):1130-1131. doi:10.1016/s0140-6736(95)91801-9

85. Hietala J, Syvälahti E, Vilkman H, et al. Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophr Res*. 1999;35(1):41-50. doi:10.1016/S0920-9964(98)00113-3

86. Dao-Castellana MH, Paillère-Martinot ML, Hantraye P, et al. Presynaptic dopaminergic function in the striatum of schizophrenic patients. *Schizophr Res*. 1997;23(2):167-174. doi:10.1016/S0920-9964(96)00102-8

87. Remy P, Samson Y, Hantraye P, et al. Clinical correlates of 18Ffluorodopa uptake in five grafted Parkinsonian patients. *Ann Neurol*. 1995;38(4):580-588. doi:10.1002/ana.410380406

88. Arai K, Sakimoto H, Urata Y, et al. Aging-Related Catatonia with Reversible Dopamine Transporter Dysfunction in Females with Depressive Symptoms: A Case Series. *Am J Geriatr Psychiatry*. 2023;31(12):1200-1205. doi:10.1016/j.jagp.2023.05.009

89. Brodnik ZD, Batra A, Oleson EB, España RA. Local GABAA Receptor-Mediated Suppression of Dopamine Release within the Nucleus Accumbens. *ACS Chem Neurosci*. 2019;10(4):1978-1985. doi:10.1021/acschemneuro.8b00268

90. Kramer PF, Twedell EL, Shin JH, Zhang R, Khaliq ZM. Axonal mechanisms mediating γ-aminobutyric acid receptor type A (GABA-A) inhibition of striatal dopamine release. Overstreet-Wadiche L, Huguenard J, Ford C, eds. *eLife*. 2020;9:e55729. doi:10.7554/eLife.55729

91. Lopes EF, Roberts BM, Siddorn RE, Clements MA, Cragg SJ. Inhibition of Nigrostriatal Dopamine Release by Striatal GABAA and GABAB Receptors. *J Neurosci*. 2019;39(6):1058-1065. doi:10.1523/JNEUROSCI.2028-18.2018

92. Ebert D, Loew T, Feistel H, Pirner A. Dopamine and depression — Striatal dopamine D2 receptor SPECT before and after antidepressant therapy. *Psychopharmacology (Berl)*. 1996;126(1):91-94. doi:10.1007/BF02246416

93. Shah PJ, Ogilvie AD, Goodwin GM, Ebmeier KP. Clinical and psychometric correlates of dopamine D2 binding in depression. *Psychol Med*. 1997;27(6):1247-1256. doi:10.1017/S0033291797005382

94. Meyer JH, McNeely HE, Sagrati S, et al. Elevated Putamen D 2 Receptor Binding Potential in Major Depression With Motor Retardation: An [11 C]Raclopride Positron Emission Tomography Study. *Am J Psychiatry*. 2006;163(9):1594-1602. doi:10.1176/ajp.2006.163.9.1594

95. Martinot MLP, Bragulat V, Artiges E, et al. Decreased Presynaptic Dopamine Function in the Left Caudate of Depressed Patients With Affective Flattening and Psychomotor Retardation. *Am J Psychiatry*. 2001;158(2):314-316. doi:10.1176/appi.ajp.158.2.314

96. SAWLE GV, HYMAS NF, LEES AJ, FRACKOWIAK RSJ. OBSESSIONAL SLOWNESS: FUNCTIONAL STUDIES WITH POSITRON EMISSION TOMOGRAPHY. *Brain*. 1991;114(5):2191-2202. doi:10.1093/brain/114.5.2191

97. Zoons E, Tijssen MAJ, Dreissen YEM, Smit M, Booij J. The Effect of Escitalopram on Central Serotonergic and Dopaminergic Systems in Patients with Cervical Dystonia, and Its Relationship with Clinical Treatment Effects: A Double-Blind Placebo-Controlled Trial. *Biomolecules*. 2020;10(6):880. doi:10.3390/biom10060880

98. Naumann M, Pirker W, Reiners K, Lange K, Becker G, Brücke T. [123I]β-CIT single-photon emission tomography in DOPA-responsive dystonia. *Mov Disord*. 1997;12(3):448-451. doi:10.1002/mds.870120330

99. Playford ED, Fletcher NA, Sawle GV, Marsden CD, Brooks DJ. Striatal (18F)dopa uptake in familial idiopathic dystonia. *Brain*. 1993;116(5):1191-1199. doi:10.1093/brain/116.5.1191

100. Niccolini F, Su P, Politis M. Dopamine receptor mapping with PET imaging in Parkinson's disease. *J Neurol*. 2014;261(12):2251-2263. doi:10.1007/s00415-014-7302-2

101. Thobois S, Prange S, Scheiber C, Broussolle E. What a neurologist should know about PET and SPECT functional imaging for parkinsonism: A practical perspective. *Parkinsonism Relat Disord*. 2019;59:93-100. doi:10.1016/j.parkreldis.2018.08.016

102. Hirose G. Drug induced parkinsonism. *J Neurol*. 2006;253(3):iii22-iii24. doi:10.1007/s00415-006-3004-8