






Reduced striatal dopamine transmission as a transdiagnostic substrate of psychomotor retardation

Ian Lam Leong,^{1,†} Tsz Huen Ng,^{2,†} Kunal Sen,^{3,†} Ella Burchill,⁴  Harry Costello,⁴ James B. Badenoch,^{5,6} Jan Coebergh,⁷ Robert A. McCutcheon,^{8,9,10} Akshay Nair,^{11,12} Michael Browning,⁸ Quentin J. M. Huys,^{4,13} Glyn Lewis,⁴  Andrew Lees,¹⁴ Anthony S. David⁴ and  Jonathan P. Rogers^{4,15}

[†]These authors contributed equally to this work.

Psychomotor retardation, defined as generalized slowing of movement and speech, is a feature of several neurological and psychiatric disorders. In this review, we discuss the hypothesis that reduced striatal dopaminergic transmission is a transdiagnostic substrate for psychomotor retardation underlying the motor features of conditions such as Parkinson's disease, drug-induced parkinsonism, neuroleptic malignant syndrome, catatonia and depression. We examine the evidence across clinical, epidemiological, neuroimaging, laboratory and therapeutic studies.

Parkinsonian disorders share slowed movement and a reduction in verbal output with catatonia and depression. Bradyphrenia, slowed cognitive processing, also occurs in Parkinson's disease and depression. In addition, there are close epidemiological relationships between depression and Parkinson's disease, and between catatonia and neuroleptic malignant syndrome.

Neuroimaging studies also generally support the association of psychomotor retardation with reduced dopaminergic transmission, particularly in the dorsal striatum. CSF measurement of homovanillic acid (a dopamine catabolite) yields inconsistent results and is non-specific. Parkinson's disease and catatonia generally respond well to dopaminergic medication. In contrast, dopamine antagonists can induce both parkinsonism and catatonia.

Our review is limited by the variability in measurement of psychomotor retardation and difficulty distinguishing between cognitive and motor slowing. It is also likely that other neurotransmitters, such as GABA and serotonin, play an important role in psychomotor speed.

It is possible that dopaminergic deficits in psychiatric disorders represent functional disruptions, in contrast to the structural damage to the substantia nigra in Parkinson's disease. We propose further research be conducted into the effects of levodopa and dopamine agonists in depression with psychomotor retardation. Alternative neuroimaging methods such as PET sequences with shorter imaging protocols and neuromelanin-MRI should also be explored.

1 Division of Psychology and Language Sciences, University College London, London WC1H 0AP, UK

2 Faculty of Education, University of Hong Kong, 999077 Hong Kong

3 Faculty of Life Sciences, University College London, London WC1E 6BT, UK

4 Division of Psychiatry, University College London, London WC1H 0AL, UK

5 Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK

6 South London and Maudsley NHS Foundation Trust, London SE5 8AZ, UK

7 Ashford St Peter's Hospital and St George's Hospitals, Ashford TW15 3AA, UK

8 Department of Psychiatry, University of Oxford, Oxford OX3 7JX, UK

9 Oxford Health NHS Foundation Trust, Oxford OX3 7JH, UK

10 Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF, UK

11 Department of Neurology, St. George's University Hospitals NHS Foundation Trust, London SW17 0QT, UK

12 Department of Neurology, City St George's University of London, London SW17 0RE, UK

13 Max Planck UCL Centre for Computational Psychiatry and Ageing Research, Department of Imaging Neuroscience, Queen Square Institute of Neurology, University College London, London WC1N 3BG, UK

14 Reta Lila Weston Institute of Neurological Studies, Queen Square Institute of Neurology, University College London, London WC1N 3BG, UK

15 Department of Neuropsychiatry, National Hospital for Neurology and Neurosurgery, London WC1N 3BG, UK

Correspondence to: Dr Jonathan Rogers
Division of Psychiatry, University College London
20 Bedford Way, London WC1H 0AL, UK
E-mail: jonathan.rogers@ucl.ac.uk

Keywords: basal ganglia; striatum; movement disorders; bradykinesia; cognitive slowing

Introduction

Psychomotor retardation (PMR) is a generalized slowing of movement and speech.^{1,2} The concept describes difficulties in initiation and maintenance of movements as well as differences between internally and externally generated thoughts or movements.^{3–5} Assessment of PMR takes into account an individual's age, culture, baseline activity and environmental factors such as temperature.

Patients with a range of psychiatric and neurological conditions present with PMR, but the term has been particularly associated with depression, especially melancholic depression.^{6,7} Given that as few as 27% of patients with depression experience remission with untargeted first-line treatment,⁸ there is an urgent need to identify why certain individuals respond to particular treatments. Uncovering transdiagnostic mechanisms for PMR could provide clinicians with novel therapies for depression and other conditions featuring PMR by repurposing medications effective in PMR for other disorders.

Central to the neuroanatomy of voluntary movement are thought to be the cortico-striato-thalamocortical circuits, particularly those involving the dorsal striatum, although the distinction from the ventral striatum is not entirely clear either in terms of cytoarchitecture or histochemistry.⁹ Structural and functional imaging, however, attest to a gradient from medial to lateral and from rostral to caudal in terms of projections from the cortex,¹⁰ which corresponds to a ventral striatum that serves limbic areas of cortex, as opposed to a dorsal striatum serving sensorimotor and associative areas.⁹ The dorsal striatum is in turn anatomically segregated by the internal capsule into the putamen and caudate (Fig. 1A). Projections from the sensorimotor cortex converge on the dorsolateral putamen and the lateral caudate nucleus, while association cortex projects to the head of the caudate and the more ventromedial putamen (Fig. 1C).^{11,12}

The mechanisms involved in programming voluntary movement are considered to involve the balance of the direct and indirect pathways of the basal ganglia. In the direct pathway, glutamate is released at the striatum, activating inhibitory GABAergic medium spiny neurons projecting to the internal globus pallidus and substantia nigra pars reticulata.^{13,14} This causes disinhibition of thalamic glutamatergic neurons that project back to the cortex and of brainstem motor regions (specifically the midbrain

locomotor region and the pedunculopontine tegmental nucleus), which are critical to posture and locomotion.^{13–16} In the indirect pathway, striatal GABAergic activity reduces the GABA output of the external globus pallidus, disinhibiting the glutamatergic neurons of the subthalamic nucleus, which excite the internal globus pallidus and substantia nigra pars reticulata.^{13,14} This increases inhibition of the thalamic neurons projecting to the cortex, reducing motion.^{13–15} Dopamine has a crucial modulatory role in both the direct and indirect pathways. Dopamine D₁ receptors (D₁Rs) are expressed at higher levels on direct pathway striatal neurons and have an excitatory effect, whereas D₂ receptors (D₂Rs) have greater expression on indirect pathway striatal neurons and have an inhibitory effect.¹⁵ A reduction in striatal dopaminergic transmission would thus increase the activity of the indirect pathway whilst decreasing activity in the direct pathway, having a dual effect of inhibiting the initiation and speed of movement. The bradykinesia of Parkinson's disease is therefore—in simple terms—conceived as overactivity of the indirect pathway relative to the direct pathway, although more complex models are being developed.¹⁷

Reduced striatal dopaminergic transmission is present in Parkinson's disease due to loss of dopaminergic neurons in the substantia nigra pars compacta.¹⁸ However, a similar functional disturbance of striatal dopamine signalling has separately been proposed to be present in catatonia,¹⁹ neuroleptic malignant syndrome,²⁰ drug-induced parkinsonism²¹ and in the pathophysiology of depression with PMR.²² In the cognitive domain, Daniel Rogers *et al.*²³ proposed that bradyphrenia (slowed cognitive processing) in Parkinson's disease and PMR in depression both involve dopaminergic dysfunction, based on a study using a computerized test showed similarities between the two. Lately, Hinkle and Pontone²⁴ have also suggested that catatonia be considered 'psychiatric parkinsonism', based on recent neuroimaging evidence.

In this paper, we present the hypothesis that reduced dopaminergic transmission in the striatum (particularly the dorsal striatum) is a transdiagnostic mechanism underlying PMR, using evidence from clinical features, epidemiology, laboratory studies and neuroimaging, as well as response to dopaminergic treatments. Integrating findings from these research modalities and relating them to developments in cognitive neuroscience, we discuss how the theory applies to conditions as diverse as Parkinson's disease,

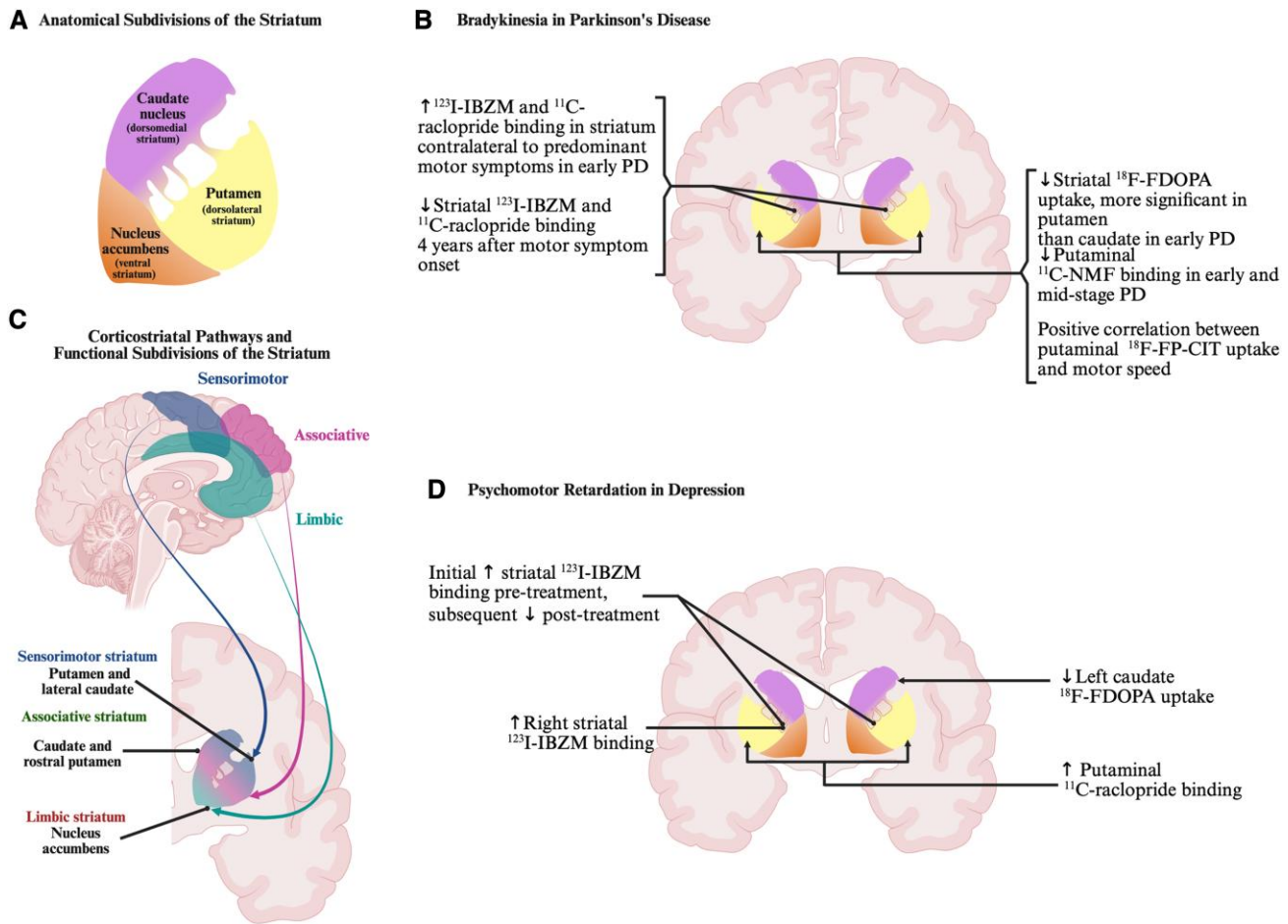


Figure 1 Anatomy and functional architecture of the striatum with relevant dopaminergic imaging findings in Parkinson's disease and depression. (A) Anatomical subdivisions of the striatum. The striatum is anatomically divided into the nucleus accumbens, caudate nucleus and putamen, the latter two being separated by the internal capsule. (B) Neuroimaging findings corresponding to bradykinesia in Parkinson's disease. A range of neuroimaging modalities implicate the striatum in the bradykinesia of Parkinson's disease and—where there is greater anatomical precision—studies have tended to emphasize the role of the putamen. (C) Corticostriatal pathways and functional subdivisions of the striatum. Most of the cortex projects to the striatum, and there is some anatomical overlap in function, but in broad terms, there is a dorsal-to-ventral gradient from sensorimotor striatum to associative striatum to limbic striatum. (D) Neuroimaging findings corresponding to psychomotor retardation in depression. Fewer studies have examined psychomotor retardation in depression, but there is converging evidence implicating the striatum, though less is known about the anatomical specificity within the striatum. $^{11}\text{C-NMF}$ = $^{11}\text{C-nomifensine}$; $^{123}\text{I-IBZM}$ = iodine-123-iodobenzamide; $^{123}\text{I-FP-CIT}$ = N - ω -fluoropropyl-2 β -carbomethoxy-3 β -(4-iodophenyl)tropane/ $^{123}\text{I-ioflupane}$; $^{18}\text{F-FDOPA}$ = 6- $^{18}\text{F-fluoro-L-3,4-dihydroxyphenylalanine}$; PD = Parkinson's disease. Created in BioRender. Leong I. (2025) <https://BioRender.com/swnk7a0>.

drug-induced parkinsonism, neuroleptic malignant syndrome, catatonia, depression and obsessional slowness.

Clinical presentation

Overlapping terminology is used to describe slowed movement and cognition in neurology and psychiatry. We present some of the commonly used terms in Table 1.

Before addressing the issue of a transdiagnostic substrate for PMR, we will examine the similarities (and differences) in clinical presentation between Parkinson's disease, where the role of dopamine is established, and other conditions where it is more speculative. Reduced dopaminergic transmission in the dorsal striatum leads to some of the cardinal motor signs of Parkinson's disease, specifically bradykinesia (slowness, with progressive decrement in amplitude and speed of self-initiated movement) and rigidity,²⁵ although its role in tremor is probably more complex.²⁶ Speech in

Parkinson's in some ways parallels the bradykinesia, in that there is a delayed onset,^{27,28} but rapid and hesitating speech may also occur,²⁹ mirroring the festinant parkinsonian gait, consisting of a progressive shortening of step length.³⁰

Bradykinesia is not specific to Parkinson's disease, but it is quite specific to reduced striatal dopamine transmission. It is a feature of related parkinsonian syndromes, such as multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration all of which have severe neuronal loss in the pars compacta of the substantia nigra, although it is not uniform and patients with supranuclear palsy seem to lack the decrement present in Parkinson's disease.^{31,32} Drug-induced parkinsonism—usually due to antagonists of the dopamine D_2R —also features bradykinesia and rigidity as important diagnostic signs.³³ Acutely, antagonists at the D_2R can occasionally trigger neuroleptic malignant syndrome, which consists of the more extreme akinesia, alongside rigidity, altered consciousness, hyperpyrexia and autonomic disturbance.^{34,35} Bradykinesia sometimes also occurs in hyperkinetic

Table 1 Terminology used for concepts related to psychomotor retardation in neurology and psychiatry

Term	Selected conditions in which it is commonly described	Definition
Psychomotor retardation	Depression, schizophrenia ^{5,20}	Generalized slowing of movement and speech ²
Bradyphrenia	Parkinson's disease, Huntington's disease ²¹	Slowing of thought ²¹
Bradykinesia	Parkinson's disease, other parkinsonisms ²²	Slowed movement with a progressive reduction in amplitude or speed ²²
Hypokinesia	Parkinson's disease, Huntington's disease, other parkinsonisms ^{23,24}	A reduction in the quantity of movement ²⁴
Catatonia	Depression, schizophrenia, NMDA receptor encephalitis ^{25,26}	A syndrome involving signs of decreased, increased or abnormal psychomotor activity, including stupor, mutism and posturing ²
Akinesia	Akinetic mutism ^{24,a}	Absence of movement ²⁴

NMDA = N-methyl-D-aspartate.

^aAkinesia has sometimes been given a more liberal definition as a synonym for bradykinesia.²⁴

disorders, such as dystonia, chorea and Huntington's disease,³⁶ although it should be noted that Huntington's disease has a different dopaminergic mechanism driven by the selective degeneration of striatal medium spiny neurons.³⁷

Psychomotor speed in depression is reduced, with meta-analytic evidence finding a standardized mean difference in actigraphically measured psychomotor speed of -0.78 (95% CI: -0.99 to -0.57) compared to healthy controls.³⁸ Between 25% and 50% of patients with depression exhibit visible PMR,³⁹ and it is strongly correlated with depression severity.⁴⁰ The PMR of depression can present very similarly to the bradykinesia of Parkinson's disease, with comparable presentations of a slow gait, hunched posture, expressionless facies, alongside slow movement and quiet speech, although usually to a lesser degree.^{41–43} The performance of patients with depression in certain cognitive tasks appears to be related to their motor slowing.²³ Perhaps an even closer comparison may be made with catatonia, a neuropsychiatric syndrome of various aetiologies, classically consisting of stupor, mutism and behavioural withdrawal.⁴⁴ A comparison of clinical features between Parkinson's disease and catatonia is shown in Table 2, illustrating similarities in muscle tone, speed and quantity of movement, facial expression, freezing episodes and altered mental status. There is an entity of excited catatonia, which may alternate with stuporous states,^{44,53} suggesting that either catatonia is not a pathophysiologically homogeneous state, or that there are rapid fluctuations in the neurochemistry of the basal ganglia. Importantly, the onset of catatonia tends to be subacute, unlike the gradual onset seen in Parkinson's disease.

Table 2 Comparison of shared clinical features between Parkinson's disease and catatonia

	Parkinson's disease ^{45–48}	Catatonia ^{47,49–52}
Motor		
Rigidity	Present, especially cogwheel rigidity, increasing with activation	Often present, but tone may also be normal or reduced. Catalepsy is highly specific.
Hypokinesia (slowed or reduced movement)	Bradykinesia, akinesia	Stupor (decreased psychomotor movement and reactivity), akinesia
Tremor	Present at rest and postural	Not typically observed
Facial manifestations	Masked facies, reduced spontaneous blink rate	Flat affect, staring, reduced blink rate
Sudden motor freezing	Freezing of gait (sudden, unwanted inability to move) typically triggered by external stimuli	Motor blocking (<i>Sperrung</i> ; abrupt cessation in voluntary movement or speech), may not have external trigger
Non-motor		
Altered mental status	Depression, apathy, anhedonia, anxiety, psychosis, impulse control disorders	Depression, mania, anxiety, psychosis

We have shown that some neurological and psychiatric conditions share PMR. Motor slowing also appears to be closely related to mental processes at the level of analysis of the individual condition. In Parkinson's disease, bradykinesia is strongly correlated with bradyphrenia—slowed cognitive processing.⁵⁴ There is, moreover, a correlation between bradykinesia and some of the affective dimensions of Parkinson's disease, specifically anhedonia and apathy.^{45–49,55} Anhedonia and apathy are both thought to be related to the dopaminergic deficits, although the specific localization is possibly more likely to be in mesocorticolimbic pathways, rather than the nigrostriatal projections thought to be responsible for bradykinesia.^{46,50–52} Cognition is also likely to be relevant to these affective states, as executive dysfunction is closely related to apathy.^{56,57} However, while bradykinesia is correlated with anhedonia and apathy, these are phenomenologically distinct concepts and do not always coexist.^{58,59}

In psychiatric conditions as well, there is evidence that PMR is closely linked to the affective state. In obsessional slowness, a severe form of obsessive-compulsive disorder, there is difficulty initiating voluntary action and often severely slowed movement.⁶⁰ In depression, PMR correlates with anhedonia,⁶¹ mirroring the association seen with bradykinesia in Parkinson's disease.

In summary, the bradykinesia seen in Parkinson's disease and other neurological movement disorders shows phenomenological similarities to the PMR of various psychiatric conditions, although subtler aspects such as the motor decrement are not clearly present

in psychiatric conditions. There is also a relationship between PMR and states such as anhedonia and apathy, which are thought to be related to reduced dopamine transmission.

Epidemiology

There is epidemiological evidence to suggest that depression is related to the development of parkinsonian disorders. Two meta-analyses have found an increased risk of subsequent Parkinson's disease in patients with depression, with an odds ratio of 2.04 (95% CI: 1.02–4.08) and relative risk of 2.20 (95% CI: 1.87–2.58), respectively.^{62,63} Intervals of between 2 and 16 years between onset of depression and Parkinson's disease diagnosis have been reported.⁶² The results of a recent Mendelian randomization study suggest that depression has a causal role in the development of Parkinson's disease.⁶⁴ The largest genome-wide association study of depression to date found that one of the genes with the strongest evidence was the dopamine receptor D₂ (*DRD2*) gene.⁶⁵ There is some evidence that PMR may constitute a genetically distinct form of depression,⁶⁶ but we are not aware of studies that have investigated whether this group is particularly at-risk for developing Parkinson's disease.

As a rarer disorder, evidence for catatonia is weaker. Catatonia has occasionally been reported to co-occur with Parkinson's disease, dementia with Lewy bodies and progressive supranuclear palsy.^{67–76} In some cases, catatonia has been reported in the context of Parkinson's disease after withdrawal of pro-dopaminergic medications.^{72,76} Parkinsonism and catatonia have also been noted to co-occur in certain genetic syndromes, including in Rett syndrome⁷⁷ and in a patient with variants of the *SHANK3* and *SYNJ1* genes.⁷⁸ These reports are suggestive but by no means conclusive.

Catatonia is, however, convincingly linked to the development of neuroleptic malignant syndrome. Catatonia may co-exist with neuroleptic malignant syndrome, and some authors have suggested that neuroleptic malignant syndrome is merely a subtype of malignant catatonia.⁷⁹ Even if one does not accept this contention—and there are features such as diaphoresis, rigor, fever and tremor that are relatively specific to neuroleptic malignant syndrome⁸⁰—the epidemiological relationship between the two conditions is compelling. Catatonia has been found to precede,⁸¹ co-exist with⁸² and follow neuroleptic malignant syndrome.^{83–85} Among 1719 patients with schizophrenia, one study found that the odds ratio for catatonia was 87.0 (95% CI 25.3–462.8) if neuroleptic malignant syndrome was present.⁸⁶ There also appears to be a spectrum between antipsychotic-induced catatonia and neuroleptic malignant syndrome.⁸⁷

In summary, depression is robustly linked to the subsequent development of Parkinson's disease. Case reports and series suggest a relationship between catatonia and various parkinsonian disorders, but there is now convincing epidemiological evidence of a relationship to neuroleptic malignant syndrome.

Laboratory evidence

Homovanillic acid (HVA) is the end-product of dopamine metabolism and can be measured in CSF as a biomarker of central dopaminergic activity.⁸⁸ HVA is reduced in Parkinson's disease^{89–91} and correlates with disease progression. A small study of neuroleptic malignant syndrome also found reduced HVA, which persisted beyond recovery, suggesting an underlying hypo-dopaminergic predisposition.⁹²

Studies on whether HVA is reduced in individuals with depression compared to healthy controls have yielded inconsistent results,^{93–96} as have those comparing depressed patients with and without a melancholic subtype.^{97,98} Two studies have examined the relationship between PMR and HVA in patients with depression, finding no correlation.^{99,100} In one study, patients with depression and PMR had lower CSF HVA concentrations than healthy controls and those with depression without PMR, but the numbers were small and did not reach statistical significance.⁹⁹ One study has found that HVA levels were positively correlated with psychomotor activity, but this included patients with depression and mania, so it is possible that the finding was driven by the latter group.¹⁰¹

In catatonia, one study found increased HVA levels relative to healthy controls.¹⁰² The same group found no relationship between an excited or retarded catatonia phenotype and HVA levels, although lorazepam responders appeared to have higher levels.¹⁰³

Before trying to interpret these findings, it is worth providing some caveats about the measurement of CSF HVA. Such measurement is neuroanatomically non-specific; that is, it does not allow us to ascertain the extent of dopamine metabolism in a particular part of the brain. Second, it is temporally non-specific; that is, it is unable to capture rapid fluctuations in dopamine metabolism, such as those that may occur during phasic release associated with certain behavioural responses.¹⁰⁴ This may be particularly relevant to psychiatric disorders, where there may be a functional dopaminergic deficit without the corresponding structural pathology in the substantia nigra that is present in Parkinson's disease.

Evidence from CSF studies strongly supports the role of dopamine in Parkinson's disease. Evidence for other conditions is much weaker, but the limitations of the method and the small studies conducted do not contradict our hypothesis. The studies do suggest that at some level the effect in depression and catatonia is different or at least more transient than in Parkinson's disease. Northoff et al.¹⁰² hypothesized that the elevated HVA levels in patients with catatonia are due to increased mesolimbic dopaminergic transmission, which in turn downregulates nigrostriatal transmission, causing catatonia. Whilst this is largely speculative, it is compatible with the neuroimaging evidence we present later in this paper.

Neuroimaging

Functional neuroimaging provides substantially more anatomical specificity than measurements of dopamine metabolites in CSF. PET and single photon emission computed tomography (SPECT) enable the quantification of dopaminergic transmission in the brain, as illustrated in Fig. 2. In ¹⁸F-FDOPA PET, radiolabelled DOPA is administered to participants and is subsequently converted by aromatic L-amino acid decarboxylase (AADC) to ¹⁸F-dopamine, which is sequestered within synaptic vesicles. Modelling of this uptake allows the calculation of the influx rate constant, K_i, that serves as a measure of presynaptic dopamine synthesis capacity.¹⁰⁵

In Parkinson's disease, there is a convergence of both post-mortem and neuroimaging studies showing that most degeneration in the nigrostriatal pathway preferentially affects the more caudolateral regions of the putamen.¹⁰⁶ Significant reductions in putaminal ¹⁸F-FDOPA uptake and putaminal ¹¹C-nomifensine (¹¹C-NMF) binding (representing nigrostriatal nerve terminal reuptake site density¹⁰⁷) correlate with the severity and lateralization of bradykinesia and rigidity.^{108–111} Relative to healthy controls,

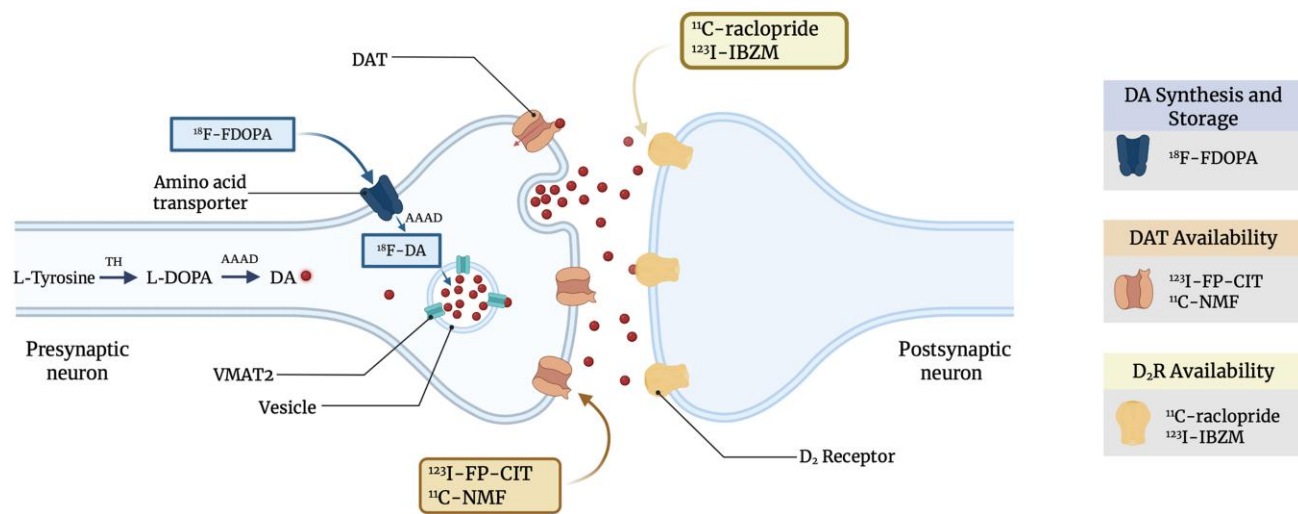


Figure 2 Simplified representation of the dopamine synthetic pathway and radioligand action sites in a striatal dopaminergic synapse. In the final two steps of the dopamine (DA) synthetic pathway, tyrosine hydroxylase (TH) converts tyrosine to L-DOPA, which is subsequently converted into DA by aromatic L-amino acid decarboxylase (AAAD). DA is stored in vesicles for tonic and phasic release. The diffusion of DA across the synaptic cleft and its binding to postsynaptic DA D₂ receptors initiates intracellular cascades in the postsynaptic neuron that enable signal transmission. Following release, dopamine transporter (DAT) facilitates the reuptake of DA into the presynaptic 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: ¹⁸F-FDOPA is taken up into the presynaptic dopaminergic neuron via an amino acid transporter, then decarboxylated by AAAD into fluorodopamine (¹⁸F-DA) and temporarily stored in vesicles. Thus, ¹⁸F-FDOPA uptake can be interpreted as an indication of presynaptic DA synthesis and storage capacity. ¹¹C-raclopride and ¹²³I-IBZM binding indicate postsynaptic D₂ receptor availability. Owing 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. AAAD = aromatic L-amino acid decarboxylase; ¹¹C-NMF = S-¹¹C-nomifensine; DA = dopamine; L-DOPA = L-3,4-dihydroxyphenylalanine/levodopa; DAT = dopamine transporters; ¹⁸F-FDOPA = 6-¹⁸F-fluoro-L-3,4-dihydroxyphenylalanine; ¹⁸F-DA = fluorodopamine; ¹²³I-FP-CIT = N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane/¹²³I-ioflupane; ¹²³I-IBZM = iodine-123-iodobenzamide; TH = tyrosine hydroxylase; VMAT2 = vesicular monoamine transporter type 2. Created in BioRender. Leong I. (2025) <https://BioRender.com/ng1udyq>.

putaminal ¹²³I-FP-CIT uptake levels (which represent density of the dopamine transporter) in patients with Parkinson's disease correlate with the mean speed and amplitude of finger tapping, while caudate uptake levels correlate with mean amplitude.¹¹²

In early Parkinson's disease, initial upregulation of striatal post synaptic D₂R shown by ¹¹C-raclopride-PET and ¹²³I-IBZM-SPECT (both of which bind to dopamine D₂/D₃ receptors) has been interpreted as a compensatory mechanism for presynaptic dopaminergic nerve terminal loss, followed by downregulation approximately 4 years following motor symptom onset.¹¹³ Though it remains difficult to ascertain whether downregulation results from disease progression or medication,¹¹⁴ consistent observations of higher striatal D₂R binding contralateral to predominant motor features suggest that the initial upregulation is a temporary compensatory response to dopamine depletion resulting from presynaptic degeneration in early Parkinson's disease.¹¹³ This is in accord with the inverse correlation observed between ¹⁸F-FDOPA uptake and ¹¹C-raclopride binding in levodopa-naïve patients with Parkinson's disease.¹¹⁵

Various lines of converging evidence suggest that a dopaminergic deficit in the sensorimotor striatum is specific to bradykinesia, rather than explanatory for all features of Parkinson's disease. An ¹⁸F-FDOPA study found that uptake in the caudate nucleus was negatively associated with measures of executive functioning.¹¹⁶ Caudate presynaptic dopaminergic nerve terminal and transporter dysfunction correlates with slower cognitive speed and impaired verbal fluency.^{116,117} Bradyphrenia appears to be correlated with ¹²³I-FP-CIT uptake in the head of the caudate.¹¹⁸ This is consistent with neuropathological findings showing reduced D1 receptor density in the caudate correlating with cognitive impairment.¹¹⁹

Anhedonia appears to involve both caudate and putaminal regions of the dorsal striatum in terms of dopamine transporter (DAT) binding.¹²⁰ Using ¹¹C-RTI-32 PET, a marker of dopamine and noradrenaline transporter binding, Remy et al.¹²¹ found a relationship between depression in Parkinson's disease and lower binding in the locus coeruleus and the ventral striatum. The pathophysiology of the parkinsonian tremor does not appear to be primarily due to a dopaminergic deficit, nor does it correlate well with bradykinesia and rigidity.¹²²⁻¹²⁴ Thus, cognitive symptoms, affective symptoms and even tremor do not appear to depend specifically on the sensorimotor striatum in Parkinson's disease in the way that bradykinesia does.

In parkinsonism secondary to dopamine antagonists, decreased ¹²³I-FP-CIT binding in the putamen (a measure of dopamine transporter availability¹²⁵) is present in a proportion of individuals¹²⁶ and predicts levodopa response and parkinsonian symptom progression,¹²⁷ with reduced putaminal ¹⁸F-FDOPA uptake observed in cases of continued or deteriorating parkinsonism post-withdrawal.¹²⁸ This suggests that parkinsonism secondary to dopamine antagonists sometimes occurs in an at-risk population with subclinical presynaptic nigrostriatal dysfunctions.¹²⁹ In neuroleptic malignant syndrome, ¹²³I-IBZM-SPECT (a measure of post synaptic D₂R density¹³⁰) reveals near-absent basal ganglia D₂R binding of the ligand in the acute phase,¹³¹ indicating dopamine antagonist occupancy of postsynaptic D₂R as a mechanism for reduced dopaminergic transmission associated with motor impairments.

Studies on catatonia mainly concentrate on presynaptic function, with limited data concerning postsynaptic D₂Rs.¹³² Three ¹⁸F-FDOPA-PET studies of individuals with psychosis have each

included a single patient with catatonia and have found decreased putaminal and caudate uptake in patients relative to other patients with schizophrenia and healthy controls,¹³³⁻¹³⁵ and comparable caudate K_i values to Parkinson's disease,¹³⁶ suggesting a similar presynaptic hypodopaminergia. Importantly, unlike D_2R ligands, ^{18}F -FDOPA does not appear to be modulated by D_2R antagonists.¹³⁷ However, it is not clear whether such observations represent a transient state or a longer-term trait. One small study of five patients suggested that dopaminergic abnormalities—at least presynaptically—are transient: five older women with catatonia and depression underwent a DAT-SPECT, which uses ^{123}I -FP-CIT-SPECT to ascertain the density of DAT in the presynaptic terminal, finding reduced binding in the striatum, which improved after treatment with benzodiazepines or electroconvulsive therapy (ECT).¹³⁸ One possible interpretation is that the reduction in DAT might be a compensatory response to reduced synaptic dopamine levels.

In depression, patients with motor retardation show lower left caudate ^{18}F -FDOPA uptake,¹³⁹ suggesting impaired presynaptic dopamine synthesis and storage. Studies investigating alterations in striatal DAT binding in depression have obtained mixed results.^{140,141} It should be noted that these studies did not specifically examine the relationship between DAT binding and PMR, and that the inconsistent findings may be due to the heterogeneity of depressed subjects included and medication effects. Studies of postsynaptic dopaminergic function in patients with depression and PMR have consistently found an increased binding of ligands to D_2R s compared to patients with depression without PMR, with studies examining striatal ^{123}I -IBZM binding¹⁴² and putaminal ^{11}C -raclopride binding.¹⁴³ Concordantly, increased right striatal ^{123}I -IBZM binding correlates positively with reaction or movement time and negatively with verbal fluency.¹⁴⁴ Given that presynaptic dopamine production is impaired, this may either represent increased availability of D_2R s due to reduced levels of the endogenous ligand, or some compensatory response to a presynaptic deficit.

Overall, neuroimaging evidence supports the hypothesis that reduced dorsal striatal dopaminergic transmission is associated with psychomotor deficits across conditions. A summary of studies is included in Table 3, while Fig. 1B and D provides a visual comparison of studies in Parkinson's disease and depression. In Parkinson's disease, there is evidence that this is mainly related to the sensorimotor striatum (predominantly the putamen), but there is insufficient evidence from other conditions to localize the deficit so precisely. Postsynaptic alterations in depression, consisting of increased binding to D_2R s, parallel the findings in early-stage Parkinson's rather than those in a later stage of the disease. Data on D_1R binding are sparse, but are perhaps less relevant, given that available PET studies examining Parkinson's disease patients typically observe no differences in striatal D_1R binding compared to healthy controls.¹⁴⁵ For Parkinson's disease and PMR in depression, there is evidence implicating the caudate and putamen, but the role of the ventral striatum has been less well characterized. Evidence for drug-induced parkinsonism, neuroleptic malignant syndrome, catatonia, obsessional slowness and hyperkinetic disorders is less comprehensive and requires further research.

Dopaminergic treatments

L-DOPA, the immediate precursor of dopamine, is the mainstay of treatment for Parkinson's disease, acting through supplementing deficient dopamine synthesis.¹⁴⁶ Other effective pharmacotherapies include dopamine agonists and monoamine oxidase

inhibitors, which inhibit dopamine catabolism.¹⁴⁷⁻¹⁵² Observational data suggest that dopamine agonists improve motivational symptoms while monoamine oxidase inhibitors improve both depressive and motivational symptoms in Parkinson's.¹⁵³ A large randomized controlled trial of the dopamine agonist pramipexole versus placebo in Parkinson's disease found an improvement in depression that was largely not mediated by improved motor symptoms.¹⁵⁴

Conversely, antipsychotics that act as antagonists at the dopamine D_2R can induce parkinsonism, with typical antipsychotics posing greater risk.²¹ Antipsychotic-induced parkinsonism can be treated with the dopamine agonist rotigotine or amantadine, which enhance dopamine synthesis and release.¹⁵⁵⁻¹⁵⁷

Neuroleptic malignant syndrome is an adverse effect of antipsychotic treatment, with typical antipsychotics and higher doses associated with increased risk.^{20,158} There is evidence that the dopamine agonist bromocriptine can be used to treat neuroleptic malignant syndrome,^{159,160} and a case series suggested levodopa may also be beneficial.¹⁶¹ Discontinuation of pro-dopaminergic medication in patients with Parkinson's disease has been shown to cause neuroleptic malignant syndrome-like symptoms (parkinsonism-hyperpyrexia syndrome).¹⁶²⁻¹⁶⁶

The use of antipsychotics in catatonia is controversial because of a frequent perceived need to treat underlying psychosis and reported benefits in such circumstances.¹⁶⁷ Aside from the risk of inducing neuroleptic malignant syndrome,⁸⁶ antipsychotics can induce or worsen catatonia, with typical antipsychotics posing a greater risk, postulated to be due to their higher affinity for D_2R .⁸⁷ Antipsychotics can simultaneously induce catatonia and parkinsonism.¹⁶⁸ Clozapine, which has a unique cholinergic mechanism and weak D_2R affinity, may be an exception that is effective in catatonia,^{169,170} with clozapine withdrawal sometimes precipitating catatonia.¹⁷¹ Conversely, initial evidence from one small human study and two animal models, suggests levodopa may be beneficial for treating catatonia, although worsening psychosis has limited its use.¹⁷²⁻¹⁷⁴ Various case reports also support the use of amantadine and methylphenidate.¹⁷⁵⁻¹⁷⁸

In depression, there is evidence for benefit in mood from several randomized controlled trials for the dopamine agonist pramipexole,^{179,180} though studies have not investigated PMR as an outcome. There is less evidence that levodopa and amineptine (a dopamine releasing agent and reuptake inhibitor¹⁸¹) are effective at alleviating PMR in depression.^{22,182-184} Bupropion, a noradrenergic and dopamine reuptake inhibitor, has evidence from numerous clinical trials supporting its superiority to placebo in depression.¹⁸⁵ Interestingly, poor mental processing speed in depression has been shown to be a predictor of strong response to the bupropion.^{186,187} Aripiprazole, a dopamine partial agonist, has evidence for augmentation of antidepressant response in treatment-resistant depression, although studies have not examined PMR specifically.¹⁸⁸ Inhibitors of monoamine oxidase A, which reduce reuptake of a range of neurotransmitters including dopamine, are also effective in depression, though little is known about predictors of response.¹⁸⁹

Another treatment predominantly used for depression that merits a mention is ECT, the use of an electrical stimulus to induce a generalized seizure.¹⁹⁰ ECT is associated with volumetric increases in the nucleus accumbens and caudate nucleus, correlating with improved PMR in depression.^{191,192} Similarly, a relative increase in metabolism in basal ganglia regions have been detected following ECT.¹⁹³ A mean reduction in striatal DAT binding of

Table 3 Summary of imaging findings by synaptic region

Condition	Presynaptic findings		Postsynaptic findings	
	Tracer	Interpretation	Tracer	Interpretation
Parkinson's disease	↓ putaminal ¹⁸ F-FDOPA uptake ¹⁻⁴ ↓ putaminal ¹¹ C-NMF binding ^{1,3} Positive correlation between putaminal ¹⁸ F-FP-CIT uptake and motor speed. ⁶	Reflects reduced presynaptic DA synthesis, storage and reuptake dysfunction Suggests reduced DA reuptake	Initial ↑ ¹²³ I-IBZM and ¹¹ C-raclopride binding in striatum contralateral to predominant motor symptoms; subsequent ↓ binding 4 years after onset ⁵	Initial ↑ D ₂ R density may be compensatory mechanism for presynaptic DA nerve terminal loss. Later ↓ density may reflect chronic under-stimulation.
Drug-induced parkinsonism	↓ putaminal ¹²³ I-FP-CIT binding ⁷ ↓ putaminal ¹⁸ F-FDOPA uptake ⁸	Suggests intrinsic ↓ in DA synthesis, which may imply that drug-induced parkinsonism tends to occur in an at-risk population with subclinical presynaptic nigrostriatal dysfunctions in DA storage and reuptake ⁹	↓ putaminal ¹¹ C-raclopride binding ¹⁰	↓ D ₂ R binding, likely reflecting receptor occupancy by medications.
Neuroleptic malignant syndrome	No studies to the authors' knowledge	No studies to the authors' knowledge	Near absent basal ganglia ¹²³ I-IBZM binding in acute phase → near-normal binding despite persistent mild parkinsonian symptoms after 4 months ¹¹	Suggests high postsynaptic D ₂ R occupancy is a mechanism for akinesia
Catatonia	↓ putaminal ^{12,13} and caudate ¹⁴ ¹⁸ F-FDOPA uptake Initial ↓ ¹²³ I-FP-CIT binding → Restored binding post- ECT/ benzodiazepine treatment ¹⁵	↓ DA synthesis and storage. Reversible ↓ in DAT capacity.	No studies to the authors' knowledge	No studies to the authors' knowledge
Psychomotor retardation in depression	↓ left caudate ¹⁸ F-FDOPA uptake in PMR patients relative to HCs and non-PMR patients ¹⁶	↓ DA synthesis and storage in left caudate	Initial ↑ striatal ¹²³ I-IBZM binding pretreatment compared to HCs and non-PMR patients; subsequent ↓ post-treatment in PMR patients relative to healthy controls and non-PMR patients ¹⁷ ↑ putaminal ¹¹ C-raclopride binding compared to HCs ¹⁸	Suggests either ↑ availability of D ₂ R due to ↓ synaptic DA levels, or a compensatory ↑ in D ₂ R density. Treatment may result in normalization.

¹¹C-NMF = ¹¹C-nomifensine; ¹⁸F-FDOPA = ¹⁸F-dihydroxyphenylalanine; ¹²³I-FP-CIT = ¹²³I-N-3-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropine; ¹²³I-IBZM-SPECT = ¹²³I-iodobenzamide single photon emission computed tomography; DA = dopamine; DAT = dopamine transporter; D₂R = dopamine D₂ receptor; ECT = electroconvulsive therapy; HC = healthy control; PMR = psychomotor retardation.

13.1% and reduced dopamine autoreceptor sensitivity following ECT are observed.^{194,195} Interestingly, ECT in Parkinson's disease transiently improves motor function, even when patients with prior psychiatric morbidity are excluded.^{196,197} However, the mechanisms of ECT remain poorly understood, likely involving multiple neurotransmitters.^{198,199}

Overall, dopamine antagonists tend to induce and worsen PMR, while it is ameliorated by medications that enhance dopamine transmission, either by increasing dopamine release or inhibiting its breakdown. However, the evidence in catatonia and depression remains preliminary with small sample sizes and a lack of well-conducted clinical trials. A summary of the impact of dopaminergic medications on different neuropsychiatric conditions is shown in Table 4. While it is plausible that ECT acts through dopaminergic mechanisms, there remains a great deal of uncertainty.

Cognitive neuroscience

We have reviewed the evidence that striatal dopamine transmission plays a transdiagnostic role in PMR, beyond the more established case of Parkinson's disease. The question remains as to whether this is plausible given what we understand about the neurobiology of dopamine transmission in the striatum.

Dopamine has a critical role in self-initiated movement across various brain regions.²⁰⁰ Rather than directly controlling fine movement kinematics, its influence lies in the initiation and execution of deliberate actions.²⁰¹ There are transient increases in nigrostriatal dopaminergic neuronal activity that consistently precede movement initiation or acceleration in mice, which correlate with the vigour of future movements.²⁰² Mesolimbic dopaminergic transmission is also key to causal learning through retrospective

Table 4 Comparison of diseases characterized by psychomotor retardation and response to dopaminergic medications

Condition	Levodopa	Dopamine agonists	Dopamine antagonists (antipsychotics)	Other
Parkinson's disease	Effective ¹⁹²	Effective ¹⁵¹⁻¹⁵³	Deleterious ^{193,194}	Monoamine oxidase inhibitors are effective ^{154,156}
Neuroleptic malignant syndrome	Effective ^{165,a}	Bromocriptine is effective ^{163,164}	Causative ¹⁶¹	—
Drug-induced parkinsonism	Ineffective ¹⁹⁵⁻¹⁹⁷	Rotigotine is effective ¹⁵⁹	Causative ¹⁶	Amantadine is effective ¹⁵⁸
Catatonias	Effective ^{175-177,a}	Ineffective ^{198,a}	Controversial ²⁵ ; clozapine may be effective ¹⁷²	Methylphenidate is effective ^{178-180,a}
Depression with psychomotor retardation	Effective ^{184-186,a}	Effective ^{157,182,a}	Aripiprazole and quetiapine are effective ^{190,199,200}	Bupropion is effective ¹⁸⁸

^aBased on limited evidence.

associations²⁰³ and prediction error calculations.²⁰⁴ The ventral tegmental area's potential downstream effects on the ventral striatum have been increasingly recognized in Parkinson's disease, particularly for non-motor symptoms.²⁰⁵ Considerable evidence indicates the nucleus accumbens as a 'limbic-motor interface' that translates motivation into action.^{206,207}

However, it is the dorsal striatum that is thought to be central in 'action-energizing' movement. Tonic dopamine levels in the dorsal striatum encode motivational signals that reflect the energetic cost of movement (i.e. the appropriate allocation of energy to match the demands of the task).²⁰⁸ Despite similar movement parameters (i.e. trajectory quality, end point accuracy, energy expenditure) to healthy controls, patients with Parkinson's disease exhibit slower movement with increased energetic demands,²⁰⁸ leading to bradykinesia being conceptualized as 'implicit' motor motivation deficits.²⁰⁹ In other words, the slow movement observed in Parkinson's disease is due to a lack of motor vigour, rather than an inability to move quickly or a simple speed-accuracy trade-off. Patients prefer slower movements because they are more sensitive to the energetic cost of faster, more demanding movements.²¹⁰ Similar impairments in depression and schizophrenia suggest that movement speed reflects implicit evaluations of movement energy costs signalled by striatal dopamine.²¹¹ Additionally, reduced dorsal striatal DAT binding, indicative of presynaptic neuronal death, is related to anhedonia and apathy.^{120,212} Considered collectively, motor speed may reflect a paucity of motivational drive.

These findings could reflect how striatal dopaminergic dysfunction affects effort-related decision-making by impairing the evaluation of motor energy costs. In Parkinson's disease, the loss of dorsal striatal dopamine function weakens the connection between motivation and movement gain.²¹³ This is consistent with the striatal dopaminergic system's role in reward-based learning, where dopaminergic neurons encode a discrepancy between expected and obtained rewards of an action.²¹⁴ This 'reward prediction error' (RPE) signal effectively guides learning until the reward gain is maximized.²¹⁵ Though these processes have typically been associated with the ventral striatum,²¹⁶ recent evidence implicates the involvement of the dorsal striatum, with the putamen and caudate nucleus potentially implicated in different roles.²¹⁷⁻²¹⁹ A gradient in the speed of reuptake of dopamine has been reported from the ventral to dorsal components of the striatum, with the dorsal striatum more sensitive to the temporally precise phasic signals and encoding prediction errors than the ventral striatum.^{220,221} The putamen appears to be important for the encoding and learning of stimulus-action associations,²²²

while the caudate nucleus is involved in the encoding of RPEs during goal-directed behaviour.²²³ These regions work in parallel to integrate sensorimotor, cognitive and motivational emotion that support action selection and initiation in goal-directed action.²²⁴⁻²²⁶ Thus, striatal dopamine release signals the value of actions, facilitating both motor learning and the invigoration of actions associated with motivationally significant outcomes, all of which are very relevant to psychiatric conditions such as depression and catatonias.

Beyond effort evaluation, decision-making about movement also involves deliberation, during which the individual evaluates different courses of action over time. Deliberation involves processes such as working memory, rule extraction and outcome prediction. Based on this definition, Pessiglione et al.²²⁷ noted a disrupted temporal uncoupling between mental deliberation and motor execution in unmedicated Parkinson's disease patients relative to healthy controls, which was reversed by levodopa but not by subthalamic nucleus deep brain stimulation. However, as this study was not accompanied by molecular imaging, the precise site and mechanisms of dopamine depletion remain unclear. The findings also led to speculation that the loss of functional segregation between basal ganglia circuits may explain the loss of temporal uncoupling between deliberation and execution, leading to decision-related hesitations being expressed as movements.

Notably, the striatal subregions may perform different functions depending on the types of stimulus inputs (e.g. conditioned versus unconditioned, external versus internal), and the parameters of motor control (e.g. large- versus small-scale, locomotion versus manipulation) being governed.²²⁸ Thus external sensory stimuli can be effective in facilitating gait initiation in Parkinson's patients with freezing of gait,²²⁹⁻²³¹ particularly visual cues in improving gait speed.^{232,233} Interestingly, it has been shown that akinetic Parkinson's patients can show a sudden temporary ability to move in situations of intense emergency, so-called 'kinesia paradoxa'.²³⁴ These findings suggest that difficulties in movement initiation could be overcome by altering the sensory input, and that the fundamental impairment in Parkinson's disease may be rooted in the execution of actions in response to the individual's intentions.²³⁵ Catatonic signs can similarly fluctuate within an illness episode.^{236,237}

There is also a reduced capacity to switch between different motor programs within a broader motor plan in Parkinson's disease.²³⁸ Specifically, impairments in sequential and simultaneous movements are more pronounced compared to individual movements.²³⁹ Therefore, the inability to switch between motor plans may be a process underlying the reduced capacity to generate

spontaneous voluntary action and the pronounced slowness in Parkinson's disease.

Relatedly, the nigrostriatal network may be implicated in the initial learning of sequential motor tasks and the memory processes enabling recall of learned motor sequences. Specifically, striatal dopaminergic transmission may be involved in the acquisition of predictive movement sequences and the efficient predictive retrieval of succeeding movements to form complete goal-oriented action sequences in monkeys.²⁴⁰ Moreover, there is evidence of striatal dopamine release during performance of a motor sequential learning task in humans. Measurements of dopamine D₂R availability by ¹¹C-raclopride have revealed that activation in the left putamen and right caudate is associated with response selection and execution, while activation in the left caudate is associated with detecting contextual changes.^{241,242} Taken together, these findings may be interpreted as a plausible explanation for the difficulties in motor plan switching experienced by patients with Parkinson's disease, and also aligns with the suggestion that striatal processing enables the 'chunking' of sequential acts into performance units.²⁴³

In summary, it is possible that dysfunction of dopaminergic transmission in the dorsal striatum (with stronger motor correlates) more directly affects movement parameters such as frequency, speed and control. In contrast, dysfunction in the ventral striatum (with stronger RPE correlates) may influence movement indirectly by affecting cognitive functions like motivation, decision-making and learning. Therefore, it may be that the striatal subregions operate hierarchically to contribute to PMR. This view may be supported by the temporal gradient in dopamine degeneration observed in Parkinson's disease, with the dorsal striatum being affected in early stages of the disease, progressing to the ventral striatum in later stages of the disease.^{244,245} However, it would be an oversimplification to associate the dorsal striatum solely with motor functions and the ventral striatum strictly with limbic or motivational functions. Ventral striatal dopaminergic depletions still impact motor parameters by reducing the overall frequency and speed of various activities. Although further research is needed to clarify the roles of these striatal subregions, dopamine transmission remains a central mechanism underlying both motor and motivational control.

Discussion

In this review, we have synthesized the evidence that reduced striatal dopamine transmission is a transdiagnostic substrate for PMR. The overlapping clinical features across conditions imply striatal dopamine as a common substrate for PMR. Epidemiological evidence indicates that transdiagnostic PMR in clinical populations may result from predisposed dopaminergic dysfunction or antidopaminergic medication effects. Molecular neuroimaging and laboratory evidence mainly associate reduced dorsal striatal transmission with PMR. Dopaminergic medication appears effective in various conditions with PMR.

Mesolimbic dopaminergic transmission is key to causal learning through retrospective associations,²⁰³ and prediction error calculations.²⁰⁴ The ventral tegmental area's potential downstream effects on the ventral striatum are increasingly recognized in Parkinson's disease, particularly in relation to cognitive and affective symptoms.²⁰⁵ Considerable evidence indicates the nucleus accumbens as a 'limbic-motor interface' that translates motivation into action.^{206,207} However, dorsal striatal dopaminergic activity remains

central for 'action-energizing' movement. Motor speed may reflect a reduction in motivational drive due to reduced striatal dopamine signalling.

Although this review has focused on dopamine, it would be an oversimplification to attribute the full spectrum of motor features of a diverse range of conditions to a single neurotransmitter. In Parkinson's disease, while it is accepted that non-dopaminergic mechanisms are central to non-motor symptoms,²⁴⁶ it is also clear that other neurotransmitters are involved in motor symptoms, although their role is probably less straightforward than that of dopamine. PET studies have found that serotonergic terminals are depleted early in the course of Parkinson's disease, supporting findings of older post-mortem studies,²⁴⁷ but serotonin transporter availability does not seem to correlate with motor symptoms.²⁴⁸ While the serotonin receptor agonist *meta*-chlorophenylpiperazine (mCPP) results in reduced locomotor activity in rodents,^{249,250} in healthy humans this effect appears to be driven primarily by cognitive slowing rather than a direct motor effect.²⁵¹ Cholinergic dysfunction has also been implicated in the motor symptoms of Parkinson's disease, but this is primarily in posture and freezing of gait, rather than in bradykinesia.²⁵² Cortical GABA levels—as measured in magnetic resonance spectroscopy—do not appear to differ between individuals with Parkinson's disease and healthy controls, but one study did find an inverse correlation between GABA in the motor cortex and motor symptoms.²⁵³

In catatonia, there is evidence both from the effectiveness of benzodiazepines²⁵⁴ and from SPECT imaging showing a reduced density of GABA-A receptors in the left sensorimotor cortex²⁵⁵ that GABA is also central to the pathophysiology. It is increasingly recognized that there are collections of neurons in the human CNS that can co-release both GABA and dopamine.²⁵⁶ In depression, it is likely that a range of monoamines are relevant²⁵⁷ and a reciprocal relationship between serotonin and dopamine release in the substantia nigra is observed.²⁵⁸ In ECT, glutamate and GABA release mediated through serotonin receptor sensitization modulates dopamine function.²⁵⁹ A pivotal role for dopamine therefore is not to the exclusion of other neurotransmitters, and there are clear relationships in the striatum between dopamine and transmitters including acetylcholine, glutamate and GABA. However, we focus on dopamine because this seems to be where the preponderance of evidence is and where there is clearest transdiagnostic relevance.

While PMR may be associated with dorsal striatal dopamine transmission downregulation, it is less clear—or less straightforward—that increased striatal dopamine transmission is linked to psychomotor agitation, as evidenced by neuroimaging findings and clinical observations of co-existing PMR and psychomotor agitation.²⁶⁰

One limitation to our findings is the heterogeneity of measurement of PMR in the evidence underpinning our review.⁶ Distinguishing cognitive from motor variables is challenging, as it introduces confounders such as executive functions, memory and attention.^{7,261} PMR scales, despite good psychometric properties, are susceptible to bias due to unnaturalistic settings.^{7,38} Actigraphy, measuring activity level over longer periods, provides a more naturalistic and objective alternative but may not correlate with other behaviours.³⁸ Advances in instrumentation and measurement modalities used in conjunction may enhance ecological validity and identify underlying brain circuitry.²⁶²

One important implication from this review is that current diagnostic classifications of psychiatric disorders may be grouping together disorders that are highly heterogeneous in their pathophysiology. Depression may or may not feature PMR.

Catatonia may present with a stuporous-retarded phenotype, but it may equally in current classifications present with an excited-agitated phenotype.^{2,44,263} We propose that future studies of psychiatric disorders with prominent motor phenotypes consider restricting their samples to a certain phenotype or stratifying the analysis by that phenotype. Given the heterogeneity of depression and low response rates to first-line therapy, the need for new and effective therapeutic interventions cannot be understated. Further studies are required to determine if PMR predicts response to dopaminergic antidepressants (e.g. bupropion and monoamine oxidase inhibitors). Although initial evidence suggests levodopa and dopamine agonists alleviate PMR in depression, recent larger studies have been retracted due to methodological issues.^{264,265} Based on our research, we propose reattempting these studies and conducting larger trials with dopamine agonists in selected populations by motor phenotype as a way of avoiding grouping patients with divergent pathophysiology. This approach may also benefit akinetic catatonia, as some evidence indicates the efficacy of levodopa and methylphenidate.^{172-174,266} ECT is recommended for patients with PMR, and/or resistant to pharmacological treatment, but is underused due to stigma.²⁶⁷⁻²⁶⁹ Further studies about its mechanism could dispel misconceptions, and dopamine transmission is a promising candidate.

Another implication concerns the imaging modalities we should consider employing in research on neuropsychiatric disorders. In Parkinson's disease, we can localize bradykinesia quite precisely to the dorsolateral striatum, although in other conditions, there is less certainty and anatomical specificity. Considering the difficulty of obtaining consent for invasive procedures and having severely unwell patients remain still in a scanner for prolonged periods, future research could explore alternative imaging methods. One option may be ¹⁸F-(E)-N-(3-iodoprop-2-enyl)-2 β -carbofluoroethoxy-3 β -(4'-methyl-phenyl) nortropine [(¹⁸F-FE-PE2I)-PET], which shows comparable sensitivity and specificity with superior striatal DAT specificity to ¹²³I-FP-CIT-SPECT.^{270,271} Its faster kinetics enable shorter intervals between injection and imaging (¹⁸F-FE-PE2I: \leq 20 min, ¹²³I-FP-CIT: \sim 30 min) and shorter static imaging protocols (16.5–42 min).^{270,272} There is also a fast ¹⁸F-DOPA PET imaging protocol,²⁷³ which may be better tolerated by unwell patients. Another option is neuromelanin MRI (NM-MRI), increasingly validated as a non-invasive, cost-effective measure of presynaptic dopaminergic neuron density and function, although it is less able to capture transient states.²⁷⁴ NM accumulates in the midbrain nuclei throughout the lifespan,²⁷⁵ reflecting a more stable marker of dopamine synthesis compared to the state-specific data from PET/SPECT.²⁷⁶ NM-MRI signals correlate with PET/SPECT measures of striatal dopamine terminal loss,²⁷⁷⁻²⁷⁹ dorsal striatal dopamine release²⁸⁰ and putaminal dopamine synthesis in Parkinson's disease,²⁸¹ showing decreased NM signal intensity in the substantia nigra pars compacta compared to healthy controls.²⁸²⁻²⁸⁵ However, its applicability in other conditions requires further research. If reduced striatal dopamine transmission accounts for PMR across conditions, similar decreases in NM signal intensity and striatal DAT binding would be expected in catatonia and some forms of depression if performed when the patient is unwell. It is not clear whether the pathology in the substantia nigra in Parkinson's disease is mirrored in other conditions featuring psychomotor retardation, which may entail functional rather than structural deficits.

The evidence examined in this narrative review generally supports reduced dorsal striatal dopamine transmission as a transdiagnostic substrate for PMR across various neurological and psychiatric conditions. That is, reduced dopamine transmission could contribute to the pathophysiology of PMR. While current

evidence is insufficient to conclusively define anatomical and mechanistic specificities, we suggest that presynaptic dysfunction in dopamine storage and reuptake in the dorsal striatum affects downstream neurotransmission, resulting in PMR. However, while the role of dopamine in Parkinson's disease is compelling, there are substantial gaps in the literature for psychiatric conditions, which could be filled by further neuroimaging and a clinical trial of a dopaminergic medication in patients with depression and PMR.

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. Future research should move beyond static models to explore striatal dopamine's role in PMR as part of a dynamic, complex system with nuanced roles of striatal subregions and the interplay with other neurotransmitter systems.

Funding

J.P.R. was funded by the Wellcome Trust (220659/Z/20/Z) and National Institute for Health and Care Research (CL-2023-18-002). I.L.L. and T.H.N. were supported by the Laidlaw Foundation. R.A.M.'s work is funded by a Wellcome Trust Clinical Research Career Development Fellowship (224625/Z/21/Z). M.B. was supported by the Government of the United Kingdom Office for Life Sciences and the National Institute for Health and Care Research (NIHR) Mental Health Translational Research Collaboration, hosted by the NIHR Oxford Biomedical Research Centre, and by the NIHR Oxford Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the National Institute for Health and Care Research or the UK Department of Health and Social Care.

Competing interests

J.P.R. reports research funding from Wellcome and NIHR; royalties from Taylor & Francis; payment for reviewing from Johns Hopkins University Press; and speaker fees from the Alberta Psychiatric Association, Grey Nuns Hospital (Edmonton), Infomed Research & Training Ltd., North East London NHS Foundation Trust and Vanderbilt University Medical Center. He is a Council member for the British Association for Psychopharmacology and a member of the Medical Advisory Board of the Catatonia Foundation. He conducts expert witness work. R.A.M. has received speaker/consultancy fees from Boehringer Ingelheim, Janssen, Karuna, Lundbeck, Newron, Otsuka, and Viatrix, and co-directs a company that designs digital resources to support treatment of mental ill health. M.B. has received consulting fees from J&J, Engrail Therapeutics, CHDR, and travel expenses from Lundbeck. He was previously employed by P1vital Ltd. All other authors report no competing interests.

Supplementary material

Supplementary material is available at [Brain](https://www.brain.oxfordjournals.org/) online.

References

1. Widlöcher DJ. Psychomotor retardation: Clinical, theoretical, and psychometric aspects. *Psychiatr Clin North Am.* 1983;6: 27-40.
2. World Health Organization (WHO). *International classification of diseases, eleventh revision (ICD-11)*. WHO;2019.

3. Walther S, Alexaki D, Weiss F, et al. Psychomotor slowing in psychosis and inhibitory repetitive transcranial magnetic stimulation. *JAMA Psychiatry*. 2024;81:563-571.
4. Osborne KJ, Walther S, Shankman SA, Mittal VA. Psychomotor slowing in schizophrenia: Implications for endophenotype and biomarker development. *Biomark Neuropsychiatry*. 2020;2:100016.
5. Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophr Bull*. 2007;33:1038-1053.
6. Bennabi D, Vandel P, Papaxanthis C, Pozzo T, Haffen E. Psychomotor retardation in depression: A systematic review of diagnostic, pathophysiologic, and therapeutic implications. *Biomed Res Int*. 2013;2013:158746.
7. Buyukdura JS, McClintock SM, Croarkin PE. Psychomotor retardation in depression: Biological underpinnings, measurement, and treatment. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:395-409.
8. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv*. 2009;60:1439-1445.
9. Haber SN, Knutson B. The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*. 2010;35:4-26.
10. Jarbo K, Verstynen TD. Converging structural and functional connectivity of orbitofrontal, dorsolateral prefrontal, and posterior parietal Cortex in the human striatum. *J Neurosci*. 2015;35:3865-3878.
11. Haber SN. Corticostriatal circuitry. *Dialogues Clin Neurosci*. 2016;18:7-21.
12. Nakano K, Kayahara T, Tsutsumi T, Ushiro H. Neural circuits and functional organization of the striatum. *J Neurol*. 2000;247:V1-V15.
13. Galvez-Jimenez N. *Scientific basis for the treatment of Parkinson's disease*. CRC Press; 2013.
14. Calabresi P, Picconi B, Tozzi A, Ghiglieri V, Di Filippo M. Direct and indirect pathways of basal ganglia: A critical reappraisal. *Nat Neurosci*. 2014;17:1022-1030.
15. Graybiel AM. The basal ganglia. *Curr Biol*. 2000;10:R509-R511.
16. Takakusaki K. Functional neuroanatomy for posture and gait control. *J Mov Disord*. 2017;10:1-17.
17. Oswal A, Cao C, Yeh CH, et al. Neural signatures of hyperdirect pathway activity in Parkinson's disease. *Nat Commun*. 2021;12:5185.
18. Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet*. 2009;373:2055-2066.
19. Gazdag G, Sienaert P. Diagnosing and treating catatonia: An update. *Curr Psychiatry Rev*. 2013;9:130-135.
20. Pileggi DJ, Cook AM. Neuroleptic malignant syndrome. *Ann Pharmacother*. 2016;50:973-981.
21. Feldman M, Marmol S, Margolesky J. Updated perspectives on the management of drug-induced parkinsonism (DIP): Insights from the clinic. *Ther Clin Risk Manag*. 2022;18:1129-1142.
22. Rampello L, Nicoletti G, Raffaele R. Dopaminergic hypothesis for retarded depression: A symptom profile for predicting therapeutic responses. *Acta Psychiatr Scand*. 1991;84:552-554.
23. 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;110:761-776.
24. Hinkle JT, Pontone GM. Reconceptualizing catatonia as "psychiatric parkinsonism". *Am J Geriatr Psychiatry*. 2023;31:1206-1208.
25. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci*. 1990;13:281-285.
26. Grafton ST. Contributions of functional imaging to understanding parkinsonian symptoms. *Curr Opin Neurobiol*. 2004;14:715-719.
27. 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;27:309-319.
28. 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;12:357-378.
29. Canter GJ. Speech characteristics of patients with Parkinson's disease: I. Intensity, pitch, and duration. *J Speech Hear Disord*. 1963;28:221-229.
30. Nonnekens J, Giladi N, Guha A, Fietzek UM, Bloem BR, Růžička E. Gait festination in parkinsonism: Introduction of two phenotypes. *J Neurol*. 2019;266:426-430.
31. Deuschländer AB, Ross OA, Dickson DW, Wszolek ZK. Atypical parkinsonian syndromes: A general neurologist's perspective. *Eur J Neurol*. 2018;25:41-58.
32. Ling H, Massey LA, Lees AJ, Brown P, Day BL. Hypokinesia without decrement distinguishes progressive supranuclear palsy from Parkinson's disease. *Brain*. 2012;135(Pt 4):1141-1153.
33. Shin HW, Chung SJ. Drug-induced parkinsonism. *J Clin Neurol*. 2012;8:15-21.
34. Factor SA. Neuroleptic malignant syndrome. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug induced movement disorders*. 2nd ed. Blackwell Publishing; 2005:174-212.
35. Addonizio G, Susman VL, Roth SD. Neuroleptic malignant syndrome: Review and analysis of 115 cases. *Biol Psychiatry*. 1987;22:1004-1020.
36. Paparella G, Fasano A, Hallett M, Berardelli A, Bologna M. Emerging concepts on bradykinesia in non-parkinsonian conditions. *Eur J Neurol*. 2021;28:2403-2422.
37. Tang TS, Chen X, Liu J, Bezprozvanny I. Dopaminergic signaling and striatal neurodegeneration in huntington's disease. *J Neurosci*. 2007;27:7899-7910.
38. Wüthrich F, Nabb CB, Mittal VA, Shankman SA, Walther S. Actigraphically measured psychomotor slowing in depression: Systematic review and meta-analysis. *Psychol Med*. 2022;52:1208-1221.
39. Sobin C, Sackeim HA. Psychomotor symptoms of depression. *Am J Psychiatry*. 1997;154:4-17.
40. Dantchev N, Widlöcher DJ. The measurement of retardation in depression. *J Clin Psychiatry*. 1998;59(Suppl 14):19-25.
41. Caligiuri MP, Ellwanger J. Motor and cognitive aspects of motor retardation in depression. *J Affect Disord*. 2000;57:83-93.
42. Rogers MA, Bradshaw JL, Pantelis C, Phillips JG. Frontostriatal deficits in unipolar major depression. *Brain Res Bull*. 1998;47:297-310.
43. Sachdev P, Aniss AM. Slowness of movement in melancholic depression. *Biol Psychiatry*. 1994;35:253-262.
44. Dawkins E, Cruden-Smith L, Carter B, et al. Catatonia psychopathology and phenomenology in a large dataset. *Front Psychiatry*. 2022;13:886662.
45. 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;17:214-220.
46. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. *Trends Neurosci*. 2012;35:68-77.
47. Cubo E, Benito-León J, Coronell C, Armesto D, on behalf of the ANIMO Study Group. Clinical correlates of apathy in patients recently diagnosed with Parkinson's disease: The ANIMO study. *Neuroepidemiology*. 2012;38:48-55.

48. Oguru M, Tachibana H, Toda K, Okuda B, Oka N. Apathy and depression in Parkinson disease. *J Geriatr Psychiatry Neurol*. 2010;23:35-41.
49. Skorvanek M, Rosenberger J, Gdovinova Z, et al. Apathy in elderly nondemented patients with Parkinson's disease: Clinical determinants and relationship to quality of life. *J Geriatr Psychiatry Neurol*. 2013;26:237-243.
50. Pagonabarraga J, Kulisevsky J, Strafella AP, Krack P. Apathy in Parkinson's disease: Clinical features, neural substrates, diagnosis, and treatment. *Lancet Neurol*. 2015;14:518-531.
51. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex–basal ganglia circuits. *Cereb Cortex*. 2006;16:916-928.
52. 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.
53. Shorter E, Fink M. *The madness of fear: A history of catatonia*. Oxford University Press; 2018.
54. Mortimer JA, Pirozzolo FJ, Hansch EC, Webster DD. Relationship of motor symptoms to intellectual deficits in Parkinson disease. *Neurology*. 1982;32:133-133.
55. Reichmann H, Brecht MH, Köster J, Kraus PH, Lemke MR. Pramipexole in routine clinical practice. *CNS Drugs*. 2003;17:965-973.
56. Butterfield LC, Cimino CR, Oelke LE, Hauser RA, Sanchez-Ramos J. The independent influence of apathy and depression on cognitive functioning in Parkinson's disease. *Neuropsychology*. 2010;24:721-730.
57. Santangelo G, Vitale C, Trojano L, et al. Relationship between depression and cognitive dysfunctions in Parkinson's disease without dementia. *J Neurol*. 2009;256:632-638.
58. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: A transdiagnostic approach. *Nat Rev Neurosci*. 2018;19:470-484.
59. Costello H, Husain M, Roiser JP. Apathy and motivation: Biological basis and drug treatment. *Annu Rev Pharmacol Toxicol*. 2024;64:313-338.
60. Ganos C, Kassavetis P, Cerdan M, et al. Revisiting the syndrome of "obsessional slowness." *Mov Disord Clin Pract*. 2015;2:163-169.
61. Lemke MR, Puhl P, Koethe N, Winkler T. Psychomotor retardation and anhedonia in depression. *Acta Psychiatr Scand*. 1999;99:252-256.
62. Bareeqa SB, Samar SS, Kamal S, et al. Prodromal depression and subsequent risk of developing Parkinson's disease: A systematic review with meta-analysis. *Neurodegener Dis Manag*. 2022;12:155-164.
63. Wang S, Mao S, Xiang D, Fang C. Association between depression and the subsequent risk of Parkinson's disease: A meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;86:186-192.
64. Du Y, Tang D, Yang G, Xu D. Depression and the risk of Parkinson's disease: A Mendelian randomization study. *Medicine (Baltimore)*. 2025;104:e41658.
65. Adams MJ, Streit F, Meng X, et al. Trans-ancestry genome-wide study of depression identifies 697 associations implicating cell types and pharmacotherapies. *Cell*. 2025;188:640-652.e9.
66. Kendler KS, Aggen SH, MC N. Evidence for multiple genetic factors underlying DSM-IV criteria for Major depression. *JAMA Psychiatry*. 2013;70:599-607.
67. Jaimes-Albornoz W, Ruiz de Pellon-Santamaria A, Nizama-Vía A, Isetta M, Albajar I, Serra-Mestres J. Catatonia in older adults: A systematic review. *World J Psychiatry*. 2022;12:348-367.
68. Trzepacz PT, Murcko AC, Gillespie MP. Progressive supranuclear palsy misdiagnosed as schizophrenia. *J Nerv Ment Dis*. 1985;173:377-378.
69. Poyraz BÇ, Aksoy Poyraz C, Yassa A, Arıkan MK, Gündüz A, Kızıltan G. Recurrent catatonia in Parkinson disease. *J Clin Psychopharmacol*. 2016;36:104-106.
70. Ramesh V, Sharma A, Sharma V, Somani A. Treatment of catatonia in Parkinson's disease with electroconvulsive therapy. *Ann Indian Acad Neurol*. 2019;22:501-503.
71. Hsu CW, Lin CC, Huang TL. A case report of intramuscular lorazepam in catatonia of a Parkinson's disease patient after deep brain stimulation. *Psychiatr Danub*. 2018;30:104-106.
72. Kamigaichi R, Kubo S, Ishikawa K, et al. Effective control of catatonia in Parkinson's disease by electroconvulsive therapy: A case report. *Eur J Neurol*. 2009;16:e6.
73. Lakshmana R, Sundram S, Cairns F. Dementia with Lewy bodies (DLB) presenting with catatonic symptoms. *Psychogeriatrics*. 2006;6:31-34.
74. Xiong GL, Palomino A, Kahn DR, Bourgeois JA. Antipsychotic induced catatonia: A case of probable dementia with Lewy bodies. *J Neuropsychiatry Clin Neurosci*. 2009;21:472-473.
75. Saito Y, Noto K, Kobayashi R, et al. Catatonia as the initial manifestation of dementia with Lewy bodies. *Am J Case Rep*. 2021;22:e932018-1-e932018-4.
76. Suzuki K, Awata S, Nakagawa K, Takano T, Matsuoka H. Catatonic stupor during the course of Parkinson's disease resolved with electroconvulsive therapy. *Mov Disord*. 2006;21:123-124.
77. Pollini L, Galosi S, Nardecchia F, et al. Parkinsonism, intellectual disability, and catatonia in a young male with MECP2 variant. *Mov Disord Clin Pract*. 2020;7:118-119.
78. Galosi S, Martinelli S, Pannone L, et al. Co-occurring SYNJ1 and SHANK3 variants in a girl with intellectual disability, early-onset parkinsonism and catatonic episodes. *Parkinsonism Relat Disord*. 2021;84:5-7.
79. Fink M. Neuroleptic malignant syndrome and catatonia: One entity or two?. *Biol Psychiatry*. 1996;39:1-4.
80. Lang FU, Lang S, Becker T, Jäger M. Neuroleptic malignant syndrome or catatonia? Trying to solve the catatonic dilemma. *Psychopharmacology (Berl)*. 2015;232:1-5.
81. Berardi D, Amore M, Keck PE, Troia M, Dell'Atti M. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome: A case-control study. *Biol Psychiatry*. 1998;44:748-754.
82. Koch M, Chandragiri S, Rizvi S, Petrides G, Francis A. Catatonic signs in neuroleptic malignant syndrome. *Compr Psychiatry*. 2000;41:73-75.
83. Caroff SN, Mann SC, Keck PEJ, Francis A. Residual catatonic state following neuroleptic malignant syndrome. *J Clin Psychopharmacol*. 2000;20:257.
84. Ihara M, Kohara N, Urano F, et al. Neuroleptic malignant syndrome with prolonged catatonia in a dopa-responsive dystonia patient. *Neurology*. 2002;59:1102-1104.
85. Carroll BT, Spetie L. Catatonia on the consultation-liaison service: A replication study. *Int J Psychiatry Med*. 1994;24:329-337.
86. Funayama M, Takata T, Koreki A, Ogino S, Mimura M. Catatonic stupor in schizophrenic disorders and subsequent medical complications and mortality. *Psychosom Med*. 2018;80:370.
87. Lee JWY. Neuroleptic-induced catatonia: Clinical presentation, response to benzodiazepines, and relationship to neuroleptic malignant syndrome. *J Clin Psychopharmacol*. 2010;30:3-10.
88. Amin F, Davidson M, Davis KL. Homovanillic acid measurement in clinical research: A review of methodology. *Schizophr Bull*. 1992;18:123-148.
89. Johansson B, Roos BE. 5-hydroxyindoleacetic and homovanillic acid levels in the cerebrospinal fluid of healthy volunteers

- and patients with Parkinson's syndrome. *Life Sci.* 1967;6:1449-1454.
90. Herbert MK, Kuiperij HB, Bloem BR, Verbeek MM. Levels of HVA, 5-HIAA, and MHPG in the CSF of vascular parkinsonism compared to Parkinson's disease and controls. *J Neurol.* 2013;260:3129-3133.
 91. Papeschi R, Molina-Negro P, Sourkes TL, Hardy J, Bertrand C. Concentration of homovanillic acid in the ventricular fluid of patients with Parkinson's disease and other dyskinesias. *Neurology.* 1970;20:991-991.
 92. Nishijima K, Ishiguro T. Clinical course and CSF monoamine metabolism in neuroleptic malignant syndrome—a study of nine typical cases and five mild cases. *Seishin Shinkeigaku Zasshi.* 1989;91:429-456.
 93. Kasa K, Otsuki S, Yamamoto M, Sato M, Kuroda H, Ogawa N. Cerebrospinal fluid gamma-aminobutyric acid and homovanillic acid in depressive disorders. *Biol Psychiatry.* 1982;17:877-883.
 94. Mitani H, Shirayama Y, Yamada T, Kawahara R. Plasma levels of homovanillic acid, 5-hydroxyindoleacetic acid and cortisol, and serotonin turnover in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006;30:531-534.
 95. Sher L, Oquendo MA, Li S, et al. Lower CSF homovanillic acid levels in depressed patients with a history of alcoholism. *Neuropsychopharmacology.* 2003;28:1712-1719.
 96. Sher L, Mann JJ, Traskman-Bendz L, et al. Lower cerebrospinal fluid homovanillic acid levels in depressed suicide attempters. *J Affect Disord.* 2006;90:83-89.
 97. Roy A, Pickar D, Linnoila M, Doran AR, Ninan P, Paul SM. Cerebrospinal fluid monoamine and monoamine metabolite concentrations in melancholia. *Psychiatry Res.* 1985;15:281-292.
 98. Yoshimura R, Okamoto N, Ikenouchi A. Comparison of plasma catecholamine metabolites in melancholic and non-melancholic depression. *Psychiatry Res Commun.* 2022;2:100063.
 99. van Praag HM, Korf J. Retarded depression and the dopamine metabolism. *Psychopharmacologia.* 1971;19:199-203.
 100. Leckman JF, Charney DS, Nelson CR, Heninger GR, Bowers MB. CSF tryptophan, 5-HIAA and hva in 132 psychiatric patients categorized by diagnosis and clinical state. In: Angrist B, Burrows GD, Lader M, Lingjaerde O, Sedvall G, Wheatley D, eds. *Recent advances in neuropsychopharmacology.* Pergamon; 1981:289-297.
 101. Post RM, Kotin J, Goodwin FK, Gordon EK. Psychomotor activity and cerebrospinal fluid amine metabolites in affective illness. *Am J Psychiatry.* 1973;130:67-72.
 102. Northoff G, Demisch L, Wenke J, Pflug B. Plasma homovanillic acid concentrations in catatonia. *Biol Psychiatry.* 1996;39:436-443.
 103. Northoff G, Wenke J, Demisch L, Eckert J, Gille B, Pflug B. Catatonia: Short-term response to lorazepam and dopaminergic metabolism. *Psychopharmacology (Berl).* 1995;122:182-186.
 104. Chaudhury D, Walsh JJ, Friedman AK, et al. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature.* 2013;493:532-536.
 105. Firmau G, Sood S, Chirakal R, Nahmias C, Garnett ES. Cerebral metabolism of 6-[¹⁸F]fluoro-l-3,4-dihydroxyphenylalanine in the primate. *J Neurochem.* 1987;48:1077-1082.
 106. Redgrave P, Rodriguez M, Smith Y, et al. Goal-directed and habitual control in the basal ganglia: Implications for Parkinson's disease. *Nat Rev Neurosci.* 2010;11:760-772.
 107. Aquilonius SM, Bertröm K, Eckernäs SÅ, et al. *In vivo* evaluation of striatal dopamine reuptake sites using 11C-nomifensine and positron emission tomography. *Acta Neurol Scand.* 1987;76:283-287.
 108. 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;113:1539-1552.
 109. Broussolle E, Dentesangle 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;166:141-151.
 110. 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;47:1290-1298.
 111. Vingerhoets FJG, Schulzer M, Calne DB, Snow BJ. Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? *Ann Neurol.* 1997;41:58-64.
 112. Lee MJ, Kim SL, Lyoo CH, Rinne JO, Lee MS. Impact of regional striatal dopaminergic function on kinematic parameters of Parkinson's disease. *J Neural Transm.* 2015;122:669-677.
 113. 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;36:1781-1791.
 114. 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;23:1-16.
 115. Sawle GV, Playford ED, Brooks DJ, Quinn N, Frackowiak RSJ. Asymmetrical presynaptic and post-synaptic changes in the striatal dopamine projection in dopa naïve parkinsonism: Diagnostic implications of the D2 receptor status. *Brain.* 1993;116:853-867.
 116. 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;57:470-475.
 117. 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;33:206.e29-206.e39.
 118. Vriend C, van Balkom TD, van Druningen C, et al. Processing speed is related to striatal dopamine transporter availability in Parkinson's disease. *Neuroimage Clin.* 2020;26:102257.
 119. Mattila PM, Røyttä M, Lönnberg P, Marjamäki P, Helenius H, Rinne JO. Choline acetyltransferase activity and striatal dopamine receptors in Parkinson's disease in relation to cognitive impairment. *Acta Neuropathol.* 2001;102:160-166.
 120. 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;94:863-870.
 121. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: Loss of dopamine and noradrenaline innervation in the limbic system. *Brain.* 2005;128:1314-1322.
 122. Pirker W. Correlation of dopamine transporter imaging with parkinsonian motor handicap: How close is it? *Mov Disord.* 2003;18(S7):S43-S51.
 123. Rossi C, Frosini D, Volterrani D, et al. Differences in nigro-striatal impairment in clinical variants of early Parkinson's disease: Evidence from a FP-CIT SPECT study. *Eur J Neurol.* 2010;17:626-630.
 124. Schiess MC, Zheng H, Soukup VM, Bonnen JG, Nauta HJW. Parkinson's disease subtypes: Clinical classification and

- ventricular cerebrospinal fluid analysis. *Parkinsonism Relat Disord.* 2000;6:69-76.
125. Neumeyer JL, Campbell A, Wang S, et al. N- Ω -fluoroalkyl analogs of (1R)-2 β -carbomethoxy-3 β -(4-iodophenyl)tropane (β -CIT): Radiotracers for positron emission tomography and single photon emission computed tomography imaging of dopamine transporters. *J Med Chem.* 1994;37:1558-1561.
 126. Tinazzi M, Ottaviani S, IU I, et al. [123 I]FP-CIT SPET imaging in drug-induced parkinsonism. *Mov Disord.* 2008;23:1825-1829.
 127. Tinazzi M, Antonini A, Bovi T, et al. Clinical and [123 I]FP-CIT SPET imaging follow-up in patients with drug-induced parkinsonism. *J Neurol.* 2009;256:910-915.
 128. Burn DJ, Brooks DJ. Nigral dysfunction in drug-induced parkinsonism: An 18 F-dopa PET study. *Neurology.* 1993;43(3_part_1):552-552.
 129. Tolosa E, Coelho M, Gallardo M. DAT imaging in drug-induced and psychogenic parkinsonism. *Mov Disord.* 2003;18(S7):S28-S33.
 130. 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.
 131. Jauss M, Krack P, Franz M, et al. Imaging of dopamine receptors with [123 I]iodobenzamide single-photon emission-computed tomography in neuroleptic malignant syndrome. *Mov Disord.* 1996;11:726-728.
 132. Haroche A, Rogers J, Plaze M, et al. Brain imaging in catatonia: Systematic review and directions for future research. *Psychol Med.* 2020;50:1585-1597.
 133. Hietala J, Syvälahti E, Vuorio K, et al. Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. *Lancet.* 1995;346:1130-1131.
 134. Hietala J, Syvälahti E, Vilkmann H, et al. Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophr Res.* 1999;35:41-50.
 135. Dao-Castellana MH, Paillère-Martinot ML, Hantraye P, et al. Presynaptic dopaminergic function in the striatum of schizophrenic patients. *Schizophr Res.* 1997;23:167-174.
 136. Remy P, Samson Y, Hantraye P, et al. Clinical correlates of 18 F-fluorodopa uptake in five grafted parkinsonian patients. *Ann Neurol.* 1995;38:580-588.
 137. Jauhar S, Veronese M, Nour MM, et al. The effects of antipsychotic treatment on presynaptic dopamine synthesis capacity in first-episode psychosis: A positron emission tomography study. *Biol Psychiatry.* 2019;85:79-87.
 138. 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;31:1200-1205.
 139. 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;158:314-316.
 140. Li Z, He Y, Tang J, Zong X, Hu M, Chen X. Molecular imaging of striatal dopamine transporters in major depression—A meta-analysis. *J Affect Disord.* 2015;174:137-143.
 141. Mizuno Y, Ashok AH, Bhat BB, Jauhar S, Howes OD. Dopamine in major depressive disorder: A systematic review and meta-analysis of in vivo imaging studies. *J Psychopharmacol.* 2023;37:1058-1069.
 142. Ebert D, Loew T, Feistel H, Pirner A. Dopamine and depression—Striatal dopamine D2 receptor SPECT before and after antidepressant therapy. *Psychopharmacology (Berl).* 1996;126:91-94.
 143. Meyer JH, McNeely HE, Sagrati S, et al. Elevated putamen D₂ receptor binding potential in major depression with motor retardation: An [11 C]raclopride positron emission tomography study. *Am J Psychiatry.* 2006;163:1594-1602.
 144. Shah PJ, Ogilvie AD, Goodwin GM, Ebmeier KP. Clinical and psychometric correlates of dopamine D₂ binding in depression. *Psychol Med.* 1997;27:1247-1256.
 145. Niccolini F, Su P, Politis M. Dopamine receptor mapping with PET imaging in Parkinson's disease. *J Neurol.* 2014;261:2251-2263.
 146. LeWitt PA. Levodopa therapy for Parkinson's disease: Pharmacokinetics and pharmacodynamics. *Mov Disord.* 2015;30:64-72.
 147. Adler CH, Sethi KD, Hauser RA, et al. Ropinirole for the treatment of early Parkinson's disease. *Neurology.* 1997;49:393-399.
 148. Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson disease. A randomized dose-ranging study. *JAMA.* 1997;278:125-130.
 149. Barone P, Bravi D, Bermejo-Pareja F, et al. Pergolide monotherapy in the treatment of early PD. *Neurology.* 1999;53:573-573.
 150. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: The TEMPO study. *Arch Neurol.* 2002;59:1937-1943.
 151. Olanow CW, Hauser RA, Jankovic J, et al. A randomized, double-blind, placebo-controlled, delayed start study to assess rasagiline as a disease modifying therapy in Parkinson's disease (the ADAGIO study): Rationale, design, and baseline characteristics. *Mov Disord.* 2008;23:2194-2201.
 152. Birkmayer W, Riederer P, Youdim MB, Linauer W. The potentiation of the antiakinetic effect after L-dopa treatment by an inhibitor of MAO-B, deprenil. *J Neural Transm.* 1975;36:303-326.
 153. Costello H, Schrag AE, Howard R, Roiser JP. Dissociable effects of dopaminergic medications on depression symptom dimensions in Parkinson disease. *Nat Ment Health.* 2024;2:916-923.
 154. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: A randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2010;9:573-580.
 155. DiMascio A, Bernardo DL, Greenblatt DJ, Marder JE. A controlled trial of amantadine in drug-induced extrapyramidal disorders. *Arch Gen Psychiatry.* 1976;33:599-602.
 156. Di Fabio R, De Filippis S, Cafariello C, et al. Low doses of rotigotine in patients with antipsychotic-induced parkinsonism. *Clin Neuropharmacol.* 2013;36:162-165.
 157. Rascol O, Fabbri M, Poewe W. Amantadine in the treatment of Parkinson's disease and other movement disorders. *Lancet Neurol.* 2021;20:1048-1056.
 158. Tse L, Barr AM, Scarapicchia V, Vila-Rodriguez F. Neuroleptic malignant syndrome: A review from a clinically oriented perspective. *Curr Neuropharmacol.* 2015;13:395-406.
 159. Mueller PS, Vester JW, Fermaglich J. Neuroleptic malignant syndrome: Successful treatment with bromocriptine. *JAMA.* 1983;249:386-388.
 160. Panagariya A, Sharma B, Singh R, Agarwal V, Dev A. The neuroleptic malignant syndrome: A report of 14 cases from north India. *Neurol India.* 2007;55:166-168.
 161. Otani K, Mihara K, Kondo T, Okada M, Kaneko S, Fukushima Y. Treatment of neuroleptic malignant syndrome with levodopa. *Hum Psychopharmacol.* 1992;7:217-221.
 162. Sechi G, Tanda F, Mutani R. Fatal hyperpyrexia after withdrawal of levodopa. *Neurology.* 1984;34:249-249.
 163. Sechi G, Manca S, Deiana GA, Corda DG, Pisu A, Rosati G. Acute hyponatremia and neuroleptic malignant syndrome in

- Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry*. 1996;20:533-542.
164. Gordon P, Frucht S. Neuroleptic malignant syndrome in advanced Parkinson's disease. *Mov Disord*. 2001;16:960-962.
165. Serrano-Dueñas M. Neuroleptic malignant syndrome-like, or —Dopaminergic malignant syndrome—Due to levodopa therapy withdrawal. Clinical features in 11 patients. *Parkinsonism Relat Disord*. 2003;9:175-178.
166. Brantley EJ, Cohn JV, Babu KM. Case files of the program in medical toxicology at brown university: Amantadine withdrawal and the neuroleptic malignant syndrome. *J Med Toxicol*. 2009;5:92-98.
167. Rogers JP, Oldham MA, Fricchione G, et al. Evidence-based consensus guidelines for the management of catatonia: Recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2023;37:327-369.
168. Gelenberg AJ, Mandel MR. Catatonic reactions to high-potency neuroleptic drugs. *Arch Gen Psychiatry*. 1977;34:947-950.
169. Saini A, Begum N, Matti J, et al. Clozapine as a treatment for catatonia: A systematic review. *Schizophr Res*. 2024;263:275-281.
170. Jann MW. Clozapine. *Pharmacotherapy*. 1991;11:179-195.
171. Lander M, Bastiampillai T, Sareen J. Review of withdrawal catatonia: What does this reveal about clozapine? *Transl Psychiatry*. 2018;8:139.
172. Bédard P, Larochelle L, Poirier LJ, Sourkes TL. Reversible effect of L-DOPA on tremor and catatonia induced by α -methyl-p-tyrosine. *Can J Physiol Pharmacol*. 1970;48:82-84.
173. Neppe VM. Management of catatonic stupor with L-dopa. *Clin Neuropharmacol*. 1988;11:90-91.
174. Singh A, Kulkarni SK. Nitecapone and selegiline as effective adjuncts to L-DOPA in reserpine-induced catatonia in mice. *Methods Find Exp Clin Pharmacol*. 2002;24:23-29.
175. Zeshan M, Majeed MH, Hanif A. Successful treatment of catatonia with methylphenidate in a 25-year-old patient with schizophrenia. *Prim Care Companion CNS Disord*. 2018;20:27487.
176. Prowler ML, Weiss D, Caroff SN. Treatment of catatonia with methylphenidate in an elderly patient with depression. *Psychosomatics*. 2010;51:74-76.
177. Neuhut R, Levy R, Kondracke A. Resolution of catatonia after treatment with stimulant medication in a patient with bipolar disorder. *Psychosomatics*. 2012;53:482-484.
178. Beach SR, Gomez-Bernal F, Huffman JC, Fricchione GL. Alternative treatment strategies for catatonia: A systematic review. *Gen Hosp Psychiatry*. 2017;48:1-19.
179. Tundo A, de Filippis R, De Crescenzo F. Pramipexole in the treatment of unipolar and bipolar depression. A systematic review and meta-analysis. *Acta Psychiatr Scand*. 2019;140:116-125.
180. Browning M, Cowen PJ, Galal U, et al. Pramipexole augmentation for the acute phase of treatment-resistant, unipolar depression: A placebo-controlled, double-blind, randomised trial in the UK. *Lancet Psychiatry*. 2025;12:579-589.
181. Ceci A, Garattini S, Gobbi M, Mennini T. Effect of long term amineptine treatment on pre- and postsynaptic mechanisms in rat brain. *Br J Pharmacol*. 1986;88:269-275.
182. Butcher LL, Engel J. Behavioral and biochemical effects of L-dopa after peripheral decarboxylase inhibition. *Brain Res*. 1969;15:233-242.
183. Goodwin F, Keith H, Brodie H, Murphy D, Bunney W. Administration of a peripheral decarboxylase inhibitor with L-DOPA to depressed patients. *Lancet*. 1970;295:908-911.
184. Goodwin FK, Sack RL. Central dopamine function in affective illness: Evidence from precursors, enzyme inhibitors, and studies of central dopamine turnover. *Adv Biochem Psychopharmacol*. 1974;12:261-279.
185. Patel K, Allen S, Haque MN, Angelescu I, Baumeister D, Tracy DK. Bupropion: A systematic review and meta-analysis of effectiveness as an antidepressant. *Ther Adv Psychopharmacol*. 2016;6:99-144.
186. Herrera-Guzmán I, Gudayol-Ferré E, Lira-Mandujano J, et al. Cognitive predictors of treatment response to bupropion and cognitive effects of bupropion in patients with major depressive disorder. *Psychiatry Res*. 2008;160:72-82.
187. Foley KF, DeSanty KP, Kast RE. Bupropion: Pharmacology and therapeutic applications. *Expert Rev Neurother*. 2006;6:1249-1265.
188. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: A multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68:843-853.
189. Suchting R, Tirumalaraju V, Gareeb R, et al. Revisiting monoamine oxidase inhibitors for the treatment of depressive disorders: A systematic review and network meta-analysis. *J Affect Disord*. 2021;282:1153-1160.
190. Espinoza RT, Kellner CH. Electroconvulsive therapy. *N Engl J Med*. 2022;386:667-672.
191. Belge JB, Van Diermen L, Schrijvers D, et al. The basal ganglia: A central hub for the psychomotor effects of electroconvulsive therapy. *J Affect Disord*. 2020;265:239-246.
192. Bouckaert F, Winter FLD, Emsell L, et al. Grey matter volume increase following electroconvulsive therapy in patients with late life depression: A longitudinal MRI study. *J Psychiatry Neurosci*. 2016;41:105-114.
193. Henry ME, Schmidt ME, Matochik JA, Stoddard EP, Potter WZ. The effects of ECT on brain glucose: A pilot FDG PET study. *J ECT*. 2001;17:33-40.
194. Masuoka T, Tateno A, Sakayori T, et al. Electroconvulsive therapy decreases striatal dopamine transporter binding in patients with depression: A positron emission tomography study with [18 F]FE-PE2I. *Psychiatry Res Neuroimaging*. 2020;301:111086.
195. Chiodo LA, Antelman SM. Electroconvulsive shock: Progressive dopamine autoreceptor subsensitivity independent of repeated treatment. *Science*. 1980;210:799-801.
196. Takamiya A, Seki M, Kudo S, et al. Electroconvulsive therapy for Parkinson's disease: A systematic review and meta-analysis. *Mov Disord*. 2021;36:50-58.
197. Andersen K, Balldin J, Gottfries C, et al. A double-blind evaluation of electroconvulsive therapy in Parkinson's disease with "ON-OFF" phenomena. *Acta Neurol Scand*. 1987;76:191-199.
198. Erchinger VJ, Erslund L, Aukland SM, Abbott CC, Oltedal L. Magnetic resonance spectroscopy in depressed subjects treated with electroconvulsive therapy—A systematic review of literature. *Front Psychiatry*. 2021;12:608857.
199. Mitchell ND, Baker GB. An update on the role of glutamate in the pathophysiology of depression. *Acta Psychiatr Scand*. 2010;122:192-210.
200. Carlsson A, Lindqvist M, Magnusson T. 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature*. 1957;180:1200-1200.
201. Costa KM, Schoenbaum G. Dopamine. *Curr Biol*. 2022;32:R817-R824.
202. da Silva JA, Tecuapetla F, Paixão V, Costa RM. Dopamine neuron activity before action initiation gates and invigorates future movements. *Nature*. 2018;554:244-248.
203. Jeong H, Taylor A, Floeder JR, et al. Mesolimbic dopamine release conveys causal associations. *Science*. 2022;378:eabq6740.

204. Eshel N, Bukwich M, Rao V, Hemmelder V, Tian J, Uchida N. Arithmetic and local circuitry underlying dopamine prediction errors. *Nature*. 2015;525:243-246.
205. Alberico SL, Cassell MD, Narayanan NS. The vulnerable ventral tegmental area in Parkinson's disease. *Basal Ganglia*. 2015;5: 51-55.
206. Mogenson GJ, Jones DL, Yim CY. From motivation to action: Functional interface between the limbic system and the motor system. *Prog Neurobiol*. 1980;14:69-97.
207. Salamone JD, Correa M, Mingote SM, Weber SM, Farrar AM. Nucleus accumbens dopamine and the forebrain circuitry involved in behavioral activation and effort-related decision making: Implications for understanding anergia and psychomotor slowing in depression. *Curr Psychiatry Rev*. 2006;2: 267-280.
208. Mazzoni P, Hristova A, Krakauer JW. Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. *J Neurosci*. 2007;27:7105-7116.
209. Chong TTJ, Bonnelle V, Manohar S, et al. Dopamine enhances willingness to exert effort for reward in Parkinson's disease. *Cortex*. 2015;69:40-46.
210. Gepshtein S, Li X, Snider J, Plank M, Lee D, Poizner H. Dopamine function and the efficiency of human movement. *J Cogn Neurosci*. 2014;26:645-657.
211. Salamone JD, Yohn SE, López-Cruz L, San Miguel N, Correa M. Activational and effort-related aspects of motivation: Neural mechanisms and implications for psychopathology. *Brain*. 2016;139:1325-1347.
212. Santangelo G, Vitale C, Picillo M, et al. Apathy and striatal dopamine transporter levels in de-novo, untreated Parkinson's disease patients. *Parkinsonism Relat Disord*. 2015; 21:489-493.
213. Mirabella G. Should I stay or should I go? Conceptual underpinnings of goal-directed actions. *Front Syst Neurosci*. 2014;8:206.
214. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997;275:1593-1599.
215. Houk JC, Adams JL, Barto AG. A model of how the basal ganglia generate and use neural signals that predict reinforcement. In: Houk JC, Davis JL, Beiser DG, eds. *Models of information processing in the basal ganglia*. MIT Press; 1994:249-270.
216. Daniel R, Pollmann S. A universal role of the ventral striatum in reward-based learning: Evidence from human studies. *Neurobiol Learn Mem*. 2014;114:90-100.
217. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. *Trends Neurosci*. 1990;13:266-271.
218. Cooper JC, Dunne S, Furey T, O'Doherty JP. Human dorsal Striatum encodes prediction errors during observational learning of instrumental actions. *J Cogn Neurosci*. 2012;24:106-118.
219. Araújo A, Duarte IC, Sousa T, et al. Neural inhibition as implemented by an actor-critic model involves the human dorsal striatum and ventral tegmental area. *Sci Rep*. 2024;14:6363.
220. Cragg SJ, Hille CJ, Greenfield SA. Dopamine release and uptake dynamics within nonhuman primate striatum *in vitro*. *J Neurosci*. 2000;20:8209-8217.
221. Cools R. Chemistry of the adaptive mind: Lessons from dopamine. *Neuron*. 2019;104:113-131.
222. Haruno M, Kawato M. Different neural correlates of reward expectation and reward expectation error in the Putamen and caudate nucleus during stimulus-action-reward association learning. *J Neurophysiol*. 2006;95:948-959.
223. Delgado MR, Miller MM, Inati S, Phelps EA. An fMRI study of reward-related probability learning. *NeuroImage*. 2005;24: 862-873.
224. Balleine BW, Delgado MR, Hikosaka O. The role of the dorsal striatum in reward and decision-making. *J Neurosci*. 2007;27: 8161-8165.
225. Koeppe MJ, Gunn RN, Lawrence AD, et al. Evidence for striatal dopamine release during a video game. *Nature*. 1998;393: 266-268.
226. Zald DH, Boileau I, El-Dearedy W, et al. Dopamine transmission in the human Striatum during monetary reward tasks. *J Neurosci*. 2004;24:4105-4112.
227. Pessiglione M, Czernecki V, Pillon B, et al. An effect of dopamine depletion on decision-making: The temporal coupling of deliberation and execution. *J Cogn Neurosci*. 2005;17: 1886-1896.
228. Salamone JD. Complex motor and sensorimotor functions of striatal and accumbens dopamine: Involvement in instrumental behavior processes. *Psychopharmacology (Berl)*. 1992;107: 160-174.
229. Burleigh-Jacobs A, Horak FB, Nutt JG, Obeso JA. Step initiation in Parkinson's disease: Influence of levodopa and external sensory triggers. *Mov Disord*. 1997;12:206-215.
230. Delval A, Tard C, Defebvre L. Why we should study gait initiation in Parkinson's disease. *Neurophysiol Clin*. 2014;44:69-76.
231. Praamstra P, Stegeman DF, Cools AR, Horstink MW. Reliance on external cues for movement initiation in Parkinson's disease. Evidence from movement-related potentials. *Brain*. 1998;121:167-177.
232. Glickstein M, Stein J. Paradoxical movement in Parkinson's disease. *Trends Neurosci*. 1991;14:480-482.
233. Russo Y, Stuart S, Silva-Batista C, Brumbach B, Vannozzi G, Mancini M. Does visual cueing improve gait initiation in people with Parkinson's disease? *Hum Mov Sci*. 2022;84:102970.
234. Bonanni L, Thomas A, Onofrj M. Paradoxical kinesia in parkinsonian patients surviving earthquake. *Mov Disord*. 2010;25: 1302-1304.
235. Robbins TW, Brown VJ. The role of the Striatum in the mental chronometry of action: A theoretical review. *Rev Neurosci*. 1990; 2:181-214.
236. Hirjak D, Rogers JP, Wolf RC, et al. Catatonia. *Nat Rev Dis Primers*. 2024;10:49.
237. Wijemanne S, Jankovic J. Movement disorders in catatonia. *J Neurol Neurosurg Psychiatry*. 2015;86:825-832.
238. Benecke R, Rothwell JC, Dick JPR, Day BL, Marsden CD. Disturbance of sequential movements in patients with Parkinson's disease. *Brain*. 1987;110:361-379.
239. Benecke R, Rothwell JC, Dick JPR, Day BL, Marsden CD. Performance of simultaneous movements in patients with Parkinson's disease. *Brain*. 1986;109:739-757.
240. Matsumoto N, Hanakawa T, Maki S, Graybiel AM, Kimura M. Role of [corrected] nigrostriatal dopamine system in learning to perform sequential motor tasks in a predictive manner. *J Neurophysiol*. 1999;82:978-998.
241. Kawashima S, Ueki Y, Kato T, Ito K, Matsukawa N. Reduced striatal dopamine release during motor skill acquisition in Parkinson's disease. *PLoS One*. 2018;13:e0196661.
242. Badgaiyan RD, Fischman AJ, Alpert NM. Striatal dopamine release in sequential learning. *NeuroImage*. 2007;38:549-556.
243. Graybiel AM. The basal ganglia and chunking of action repertoires. *Neurobiol Learn Mem*. 1998;70:119-136.
244. Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the Striatum of patients with idiopathic Parkinson's disease. *N Engl J Med*. 1988;318:876-880.
245. Morrish PK, Sawle GV, Brooks DJ. An [¹⁸F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. *Brain*. 1996;119:585-591.

246. Chaudhuri KR, Healy DG, Schapira AHV. National institute for clinical excellence. Non-motor symptoms of Parkinson's disease: Diagnosis and management. *Lancet Neurol*. 2006;5:235-245.
247. Politis M, Loane C. Serotonergic dysfunction in Parkinson's disease and its relevance to disability. *ScientificWorldJournal*. 2011;11:1726-1734.
248. Politis M, Wu K, Loane C, et al. Staging of serotonergic dysfunction in Parkinson's disease: An in vivo 11C-DASB PET study. *Neurobiol Dis*. 2010;40:216-221.
249. Gleason SD, Shannon HE. Meta-chlorophenylpiperazine induced changes in locomotor activity are mediated by 5-HT1 as well as 5-HT2C receptors in mice. *Eur J Pharmacol*. 1998;341:135-138.
250. Lucki I, Ward HR, Frazer A. Effect of 1-(m-chlorophenyl)piperazine and 1-(m-trifluoromethylphenyl)piperazine on locomotor activity. *J Pharmacol Exp Ther*. 1989;249:155-164.
251. Sabbe B, Hulstijn W, Maes M, Pier M, Scharpé S, Zitman F. Psychomotor slowing, neuroendocrine responses, and behavioral changes after oral administration of meta-chlorophenylpiperazine in normal volunteers. *Psychiatry Res*. 2001;105:151-163.
252. Bohnen NI, Yarnall AJ, Weil RS, et al. Cholinergic system changes in Parkinson's disease: Emerging therapeutic approaches. *Lancet Neurol*. 2022;21:381-392.
253. van Nuland AJM, den Ouden HEM, Zach H, et al. GABAergic changes in the thalamocortical circuit in Parkinson's disease. *Hum Brain Mapp*. 2020;41:1017-1029.
254. Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. II. Treatment with lorazepam and electroconvulsive therapy. *Acta Psychiatr Scand*. 1996;93:137-143.
255. Northoff G, Steinke R, Czercvenka C, et al. Decreased density of GABA-A receptors in the left sensorimotor cortex in akinetic catatonia: Investigation of in vivo benzodiazepine receptor binding. *J Neurol Neurosurg Psychiatry*. 1999;67:445-450.
256. Tritsch NX, Granger AJ, Sabatini BL. Mechanisms and functions of GABA co-release. *Nat Rev Neurosci*. 2016;17:139-145.
257. Hasler G. Pathophysiology of depression: Do we have any solid evidence of interest to clinicians? *World Psychiatry*. 2010;9:155-161.
258. Hsiao JK, Potter WZ, Agren H, Owen RR, Pickar D. Clinical investigation of monoamine neurotransmitter interactions. *Psychopharmacology (Berl)*. 1993;112:S76-S84.
259. Kritzer MD, Peterchev AV, Camprodon JA. Electroconvulsive therapy: Mechanisms of action, clinical considerations, and future directions. *Harv Rev Psychiatry*. 2023;31:101-103.
260. Cavanna AE, Robertson MM, Critchley HD. Catatonic signs in Gilles de la Tourette syndrome. *Cogn Behav Neurol*. 2008;21:34-37.
261. Pier MPBI, Hulstijn W, Sabbe BGC. Differential patterns of psychomotor functioning in unmedicated melancholic and nonmelancholic depressed patients. *J Psychiatr Res*. 2004;38:425-435.
262. Walther S, Bernard JA, Mittal VA, Shankman SA. The utility of an RDoC motor domain to understand psychomotor symptoms in depression. *Psychol Med*. 2019;49:212-216.
263. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5-TR*. American Psychiatric Association Publishing; 2022.
264. Rutherford BR, Slifstein M, Chen C, et al. Effects of L-DOPA monotherapy on psychomotor speed and [11C]raclopride binding in high risk depressed older adults. *Biol Psychiatry*. 2019;86:221-229.
265. Rutherford BR, Choi J, Slifstein M, et al. Neuroanatomical predictors of L-DOPA response in older adults with psychomotor slowing and depression: A pilot study. *J Affect Disord*. 2020;265:439-444.
266. Starkstein SE, Petracca G, Tesón A, et al. Catatonia in depression: Prevalence, clinical correlates, and validation of a scale. *J Neurol Neurosurg Psychiatry*. 1996;60:326-332.
267. Lloyd JR, Silverman ER, Kugler JL, Cooper JJ. Electroconvulsive therapy for patients with catatonia: Current perspectives. *Neuropsychiatr Dis Treat*. 2020;16:2191-2208.
268. Sackeim HA. Modern electroconvulsive therapy: Vastly improved yet greatly underused. *JAMA Psychiatry*. 2017;74:779-780.
269. Salani D, Goldin D, Valdes B, DeSantis J. Electroconvulsive therapy for treatment-resistant depression: Dispelling the stigma. *J Psychosoc Nurs Ment Health Serv*. 2023;61:11-17.
270. Jakobson MS, Axelsson J, Jonasson L, et al. Dopamine transporter imaging with [¹⁸F]FE-PE2I PET and [¹²³I]FP-CIT SPECT-A clinical comparison. *EJNMMI Res*. 2018;8:100.
271. Marner L, Korsholm K, Anderberg L, et al. [18F]FE-PE2I PET is a feasible alternative to [123I]FP-CIT SPECT for dopamine transporter imaging in clinically uncertain parkinsonism. *EJNMMI Res*. 2022;12:56.
272. Sonni I, Fazio P, Schain M, et al. Optimal acquisition time window and simplified quantification of dopamine transporter availability using ¹⁸F-FE-PE2I in healthy controls and Parkinson disease patients. *J Nucl Med*. 2016;57:1529-1534.
273. Veronese M, Santangelo B, Jauhar S, et al. A potential biomarker for treatment stratification in psychosis: Evaluation of an [18F]FDOPA PET imaging approach. *Neuropsychopharmacology*. 2021;46:1122-1132.
274. Trujillo P, Aumann MA, Claassen DO. Neuromelanin-sensitive MRI as a promising biomarker of catecholamine function. *Brain*. 2024;147:337-351.
275. Zecca L, Fariello R, Riederer P, Sulzer D, Gatti A, Tampellini D. The absolute concentration of nigral neuromelanin, assayed by a new sensitive method, increases throughout the life and is dramatically decreased in Parkinson's disease. *FEBS Lett*. 2002;510:216-220.
276. Kashihara K, Shinya T. Neuromelanin magnetic resonance imaging of nigral volume loss in patients with Parkinson's disease. *J Clin Neurosci*. 2011;18:1093-1096.
277. Isaias IU, Trujillo P, Summers P, et al. Neuromelanin imaging and dopaminergic loss in Parkinson's disease. *Front Aging Neurosci*. 2016;8:196.
278. Kuya K, Shinohara Y, Miyoshi F, Fujii S, Tanabe Y, Ogawa T. Correlation between neuromelanin-sensitive MR imaging and 123I-FP-CIT SPECT in patients with parkinsonism. *Neuroradiology*. 2016;58:351-356.
279. Ryman SG, Poston KL. MRI biomarkers of motor and non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord*. 2020;73:85-93.
280. Cassidy CM, Zucca FA, Girgis RR, et al. Neuromelanin-sensitive MRI as a noninvasive proxy measure of dopamine function in the human brain. *Proc Natl Acad Sci U S A*. 2019;116:5108-5117.
281. Depierreux F, Parmentier E, Mackels L, et al. Parkinson's disease multimodal imaging: F-DOPA PET, neuromelanin-sensitive and quantitative iron-sensitive MRI. *NPJ Parkinsons Dis*. 2021;7:57.
282. Cho SJ, Bae YJ, Kim JM, et al. Diagnostic performance of neuromelanin-sensitive magnetic resonance imaging for patients with Parkinson's disease and factor analysis for its heterogeneity: A systematic review and meta-analysis. *Eur Radiol*. 2021;31:1268-1280.
283. Ohtsuka C, Sasaki M, Konno K, et al. Changes in substantia nigra and locus coeruleus in patients with early-stage Parkinson's disease using neuromelanin-sensitive MR imaging. *Neurosci Lett*. 2013;541:93-98.

284. Ohtsuka C, Sasaki M, Konno K, et al. Differentiation of early-stage parkinsonisms using neuromelanin-sensitive magnetic resonance imaging. *Parkinsonism Relat Disord*. 2014; 20:755-760.
285. Wang L, Yan Y, Zhang L, Liu Y, Luo R, Chang Y. Substantia nigra neuromelanin magnetic resonance imaging in patients with different subtypes of Parkinson disease. *J Neural Transm*. 2021;128:171-179.