Reduced Striatal Dopamine Transmission as a Transdiagnostic Mechanism for Psychomotor Retardation

Ian Lam (Cheryl) Leong, Kunal Sen, Tsz Huen (Adrienne) Ng, Jonathan Rogers

UCL Division of Psychological and Language Sciences, Division of Biosciences, Division of Psychiatry; University of Hong Kong

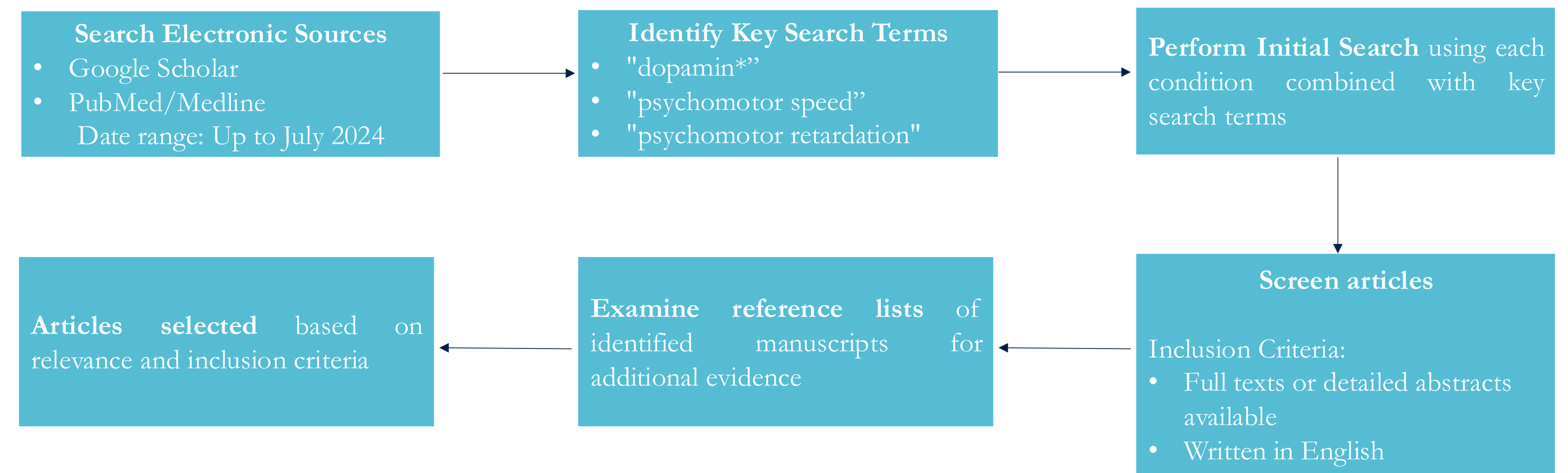
Background

- **Psychomotor retardation** (PMR; visible slowing of speech and movement) is a feature of several neurological and psychiatric disorders
- Previous research has indicated that both neurological and psychiatric causes of PMR share **disruptions in dopaminergic transmission**

Objective: To conduct a narrative review to evaluate the hypothesis that **reduced striatal dopamine transmission is a transdiagnostic mechanism underlying PMR across various neurological and psychiatric disorders** (Parkinson's Disease, Parkinson's plus syndromes, drug-induced parkinsonism, neuroleptic malignant syndrome, catatonia, PMR in depression, obsessional slowness, hyperkinetic disorders)

Aims:
- To increase the **anatomical and mechanistic specificity** in describing the role of **striatal dopamine transmission** in disease pathophysiology, in terms of synaptic location (pre/post), component (nerve terminal/transporter/receptor) and function (storage/reuptake/binding)
  - Significant implications for **repurposing dopaminergic drug treatments**, promoting more **personalised treatments**

Method



Distribution of Responsibilities:
- JR conceptualised the review, secured funding and led the writing of the original draft
- ILL: Clinical features and neuroimaging; created relevant tables and the striatal dopaminergic synapse illustration, wrote the discussion and synthesised it with the work of THN and KS
- KS: Laboratory evidence and dopaminergic medications, wrote the introduction and abstract.
- THN: epidemiology and electroconvulsive therapy, formatted the manuscript.

Clinical Features

- Evidence suggests that **neurological conditions present comparable clinical features to psychiatric conditions**
- Catatonia shares many symptoms with Parkinson's disease (e.g. rigidity, hypokinesia, sudden motor freezing, altered mental status)
- Potential relationship between PMR in depression and bradykinesia and bradyphrenia in Parkinson's disease
  - Similar clinical presentations: slow, shuffling gait, hunched posture, expressionless and static-masked facies, decrease in speech speed and volume
- **Nigrostriatal dopaminergic deficiency likely contributes to *both* motor** (bradykinesia, rigidity) **and cognitive** (bradyphrenia: slowed cognitive processing) **symptoms** across neurological and psychiatric conditions

Epidemiology

- PMR **strongly correlates** with depression severity
- Meta-analyses show an **increased risk of subsequent Parkinson's disease** in patients with **depression**
- Depression may be a **prodromal symptom** or a **causal risk** factor for Parkinson's disease
  - Either would be compatible with a **shared hypodopaminergic pathophysiology**
- PMR may result from **predisposed dopaminergic dysfunction** or **antipsychotic use** (also affects dopamine transmission)

Laboratory Evidence

- **Homovanillic acid** (HVA), a dopamine metabolism product, serves as a potential **biomarker for brain dopamine levels**
- **Cerebrospinal fluid (CSF) dopamine and HVA levels decrease** with Parkinson's disease progression
- Autopsies and lumbar puncture studies show **reduced striatal dopamine and CSF HVA levels** in various forms of Parkinson's plus syndromes
- **Inconsistent results** regarding whether patients with depression have different CSF HVA levels compared to healthy controls and whether levels correlate with psychomotor activity
- Laboratory studies **generally indicate reduced dopaminergic transmission in PMR**, but not in hyperkinetic disorders (dystonia, chorea, mania, tic disorders)
- Note that CSF or plasma HVA levels **do not indicate dopaminergic transmission location** and **may not significantly correlate** with basal ganglia HVA levels – findings should be cautiously interpreted

Neuroimaging

- PET and single photon emission computed tomography (SPECT) quantify dopaminergic transmission in the brain (see ***Figure 1*** for schematic representation and imaging radioligand action sites)
- Neuroimaging evidence **predominantly supports associations between reduced dorsal striatal dopaminergic transmission and psychomotor deficits across conditions**
- ***Compromised* nigrostriatal pre-synaptic dopamine storage and reuptake capacity** contribute to motor and non-motor symptoms in Parkinson's Disease
- ***Impaired* dopamine storage in pre-synaptic nerve terminals and reduced striatal post-synaptic D2 receptor availability** are associated with PMR in depression
- Sufficient evidence available to specify subregional dopaminergic differences for Parkinson's disease and PMR in depression; other conditions require further research

Dopaminergic Medications

- **Levodopa** (dopamine's immediate precursor) and **dopamine agonists** (activates dopamine receptors) are forms of dopaminergic medications effective in alleviating Parkinson's disease symptoms via **replacement of striatal dopamine action**
- However, these medications have limited efficacy in treating forms of Parkinson's plus syndromes
- Levodopa may help alleviate PMR in depression, psychomotor symptoms in neuroleptic malignant syndrome and catatonia
- Medication reducing dopaminergic activity is generally effective for hyperkinetic disorders
- **Dopaminergic medications appear to be effective in a range of disorders with PMR, though some inconsistencies exist**
- **Future research** should focus on understanding the **action mechanism of dopaminergic medications**

Electroconvulsive Therapy

- **Electroconvulsive therapy** (ECT) is a treatment that involves using an **electrical stimulus to induce a generalised seizure**
- **Highly effective for treating depression**; PMR is a significant predictor of favourable ECT response in terms of symptom reduction and remission
- Average decrease in striatal DAT binding and reduced dopamine autoreceptor sensitivity following ECT is observed
- **Patients with Parkinson's disease show marked improvements in motor, depressive and psychotic symptoms following ECT**
- ECT's efficacy is less consistent for drug-induced parkinsonism, tardive dystonia and tardive dyskinesia; limited studies for catatonia and neuroleptic malignant syndrome
- **Therapeutic mechanisms remain unclear** and require further investigation; **striatal dopamine seems pivotal**, though other mechanisms may be involved

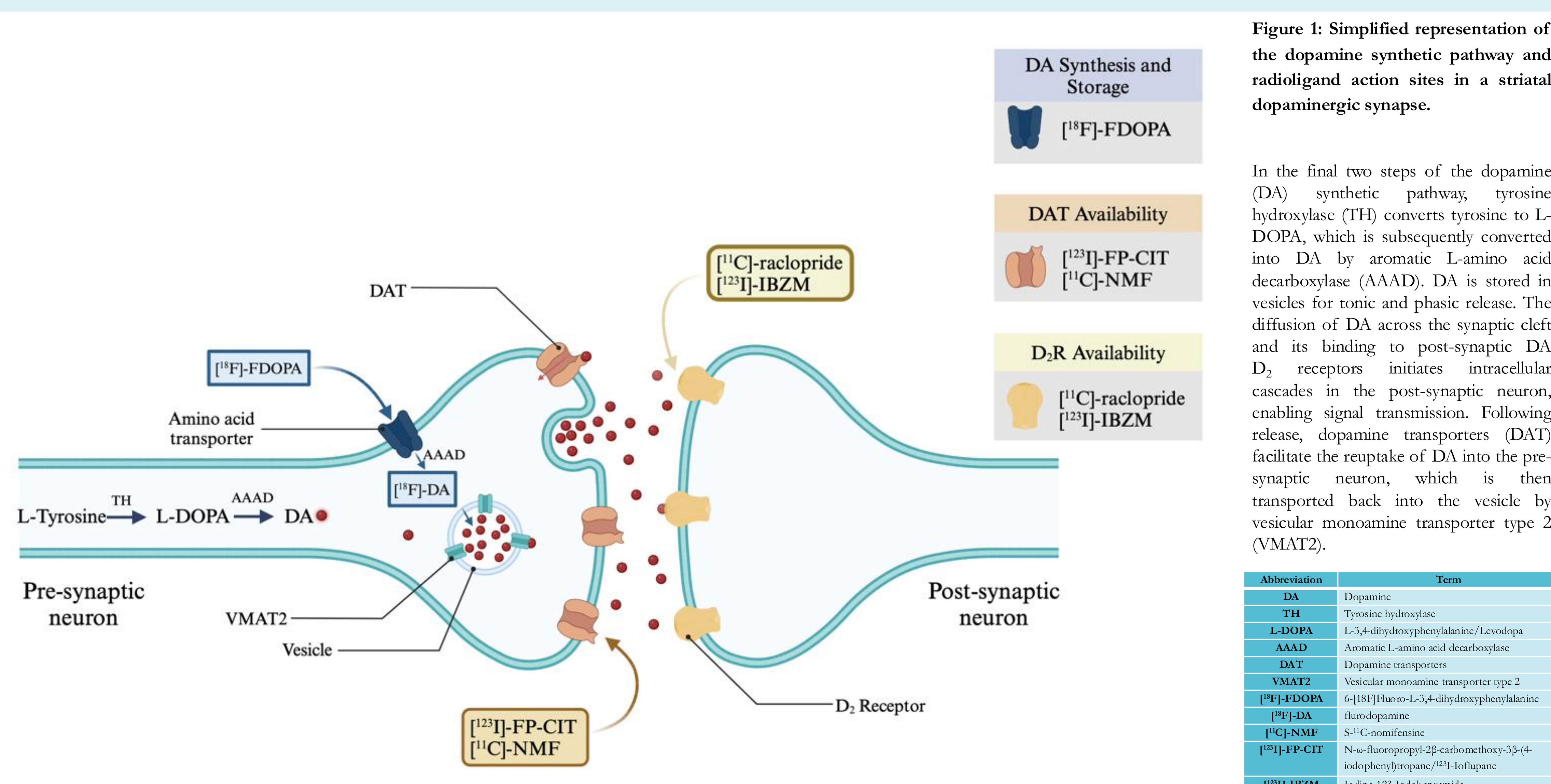


Figure 1: Simplified representation of the dopamine synthetic pathway and radioligand action sites in a striatal dopaminergic synapse.

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

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

Discussion

- **Evidence generally supports** reduced dorsal striatal dopamine transmission as a transdiagnostic mechanism underlying PMR
- Increased striatal dopamine transmission is not directly linked to psychomotor agitation
- **More evidence available for psychomotor complications in Parkinson's disease, Parkinson's plus syndromes and PMR in depression**, less compelling for other disorders
- **Motor speed may reflect a paucity of motivational drive**
  - dorsolateral striatal dopaminergic activity is central for "action-energising" movement – potential conceptualisation of bradykinesia and rigidity in Parkinson's disease as **"implicit" motor motivation deficits**
- **The complete range of motor and cognitive symptoms should not be solely attributed to dopamine**
- **High heterogeneity PMR measurement** impacts the quality of evidence in our review
- Heterogenous symptoms of psychiatric disorders complicate accurate diagnostic thresholds and patient selection for clinical trials
- Explore alternative imaging methods such as **non-invasive** neuromelanin MRI and PET sequences with **shorter imaging protocols**

For further information, please email: cheryl.leong.23@ucl.ac.uk

Please scan the QR code for the Bibliography

Figure 1 created with Biorender.com

LAIDLAW FOUNDATION