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REVIEW ARTICLE

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Impulse control disorder, lysosomal malfunction and ATP13A2 insufficiency in Parkinsonism

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Abstract

Lysosomal transport of cargos in neurons is essential for neuronal proteostasis, transmission and functional motors and behaviours. Lysosomal malfunction including storage disorders is involved in the pathogenesis of Parkinson's disease (PD). Given the unclear molecular mechanisms of diverse defects in PD phenotypes, especially behavioural deficits, this mini review explores the cellular contexts of PD impulse control disorders and the molecular aspects of lysosomal cross-membrane transports. Focuses are paid to trace metal involvements in α-synuclein assembly in Lewy bodies, the functions and molecular interactions of ATP13A2 as ATPase transporters in lysosomal membranes for cross-membrane trafficking and lysosomal homeostasis, and our current understandings of the neural circuits in ICD. Erroneously polarized distributions of cargos such as metals and lipids on each side of lysosomal membranes triggered by gene mutations and deregulated expression of ATP13A2 may thus instigate sensing protein structural changes such as aggregations, organelle degeneration, and specific neuronal ageing and death in Parkinsonism.

KEYWORDS
hypersexuality, impulse control disorder, lysosome transport, skin picking, trace metals, trichotillomania

1 | INTRODUCTION

Parkinson's disease (PD) characteristic of movement disorders (resting tremor, rigidity, bradykinesia or gait disorders) is a common degenerative disease of the nervous system following the senile dementia caused by chronic lesion of the central nervous system (CNS). Numerous studies have shown that the pathological basis of PD is related to dopamine (DA) neuronal degenerative injury in midbrain substantia nigra (SN). The progressive neurodegeneration of specific brain regions has been shown to be associated with eosinophilic inclusions (Lewy bodies) in the neurons, resulting in reduced levels of DA in the striatum, loss of neuronal function, degeneration and death. Although dopaminergic neurotransmitter therapy can cause partial remission, it can also cause side effects including behavioural abnormalities.[1,2]

Parkinson's disease patients present the symptoms of behavioural disorder that include excessive eating, frequent sexual activity and other compulsive actions, characteristic of involuntary impulse control disorders that are clinically known as the impulse control disorder (ICD).[2-4] Although its pathogenesis is unknown, ICD has been reported to be a common behavioural disorder accounting for 3% of adults usually in the youth stage[5] and 25%-50% in PD patients.[6-8] Clinical diagnosis of ICD depends on interrogation assessment, and apparently there is no effective treatment.[6-8] Understanding of the pathological changes of PD and ICD involves clarification of the concurrences of abnormal behaviour and movement mediated by convergent interactions between genetic and environmental factors on specified neurotransmitter circuits of particular brain regions.

2 | THE CHARACTERISTICS OF PD ICD

Impulsive control of behaviour is an important mechanism in the regulation of human and animal physiological behaviours, and is the result of the survival and evolution of social animals. For centuries, people

have been puzzled of the abnormal behaviours of impulsive control.[5] Although common in young people, excessive impulse also occurs in adulthood and even lasts for a lifetime as ICD syndrome.[6-8] The spectrums of ICD include more mating behaviour, more eating, hair pulling disorder (trichotillomania, TTM), nail biting (onychophagia) and skin picking disorder (dermatillomania).[3,9-15] Whereas the predominant symptoms in males appear to be hypersexuality,[8,9,16-20] female patients commonly show TTM, nail biting and or skin picking.[21-25] Intriguingly, PD patients with ICD are usually young having familial PD, neuropsychiatric disorders or gambling history,[3] and can have two or more ICD symptoms coexisting.[19,20,26]

The genetic and molecular features of PD ICD are unknown. Studies suggest that ICD pathogenesis is related to a dysfunction of the neural circuits involving the prefrontal cortex (or orbital front cortex, OFC) and the striatum. Neural imaging studies of PD patients showed ventral OFC dysfunctions[2,27-29] with attenuated activity of OFC in a top-down control pathway.[30] In addition, the striatal ventral limbic system appears hyperactivity leading to hyper-impulsive signals.[31] Measuring neurotransmissions suggests that in the OFC, decreased serotonin (5-HT) results in weakened inhibition over impulses for incentives.[32,33] The repression known as reversal learning is an essential mechanism of behavioural flexibility, which depends on the integrity of the OFC-striatal circuit. The selective serotonin reuptake inhibitor (SSRI) fluoxetine inhibition of 5-HT synaptic reuptake has been demonstrated to increase reverse learning and relieve ICD symptoms.[27,32-36]

A major issue in the use of dopamine to treat PD is a resultant increase in ICD, suggesting that increased DA receptor activity in the brain limbic system is associated with ICD.[1,26] Some studies have shown that D3 receptor activity is involved in mediating ICD,[37] although others suggest that it requires further study to confirm.[38,39] In addition, increased glutamate may be involved in connecting amygdale, hypothalamus, cingulate gyrus and OFC to promote hypersexuality,[40-42] repeated hair pulling[43,44] and anxiety.[45] Thus, the regulation by 5-HT receptors activity in the OFC of dopamine and/or glutamate activities in the ventral striatum and cingulate regions may be a part of the mechanism of impulse regulation over reward-entrancing behaviours.

3 | LEWY BODIES, α-SYNUCLEIN AND CU^{2+}

Neural degeneration selectively occurs to certain populations of neurons e.g. in the midbrain regions or OFC, and is accountable for the diversity of PD pathology including that of ICD. These neurons are particularly sensitive to intracellular toxic environments of aberrant accumulations of denatured macromolecules, as undertaking premature aging. Lewy bodies represent such intracellular toxic macromolecular aggregates of α-synuclein as a fundamental molecular pathology of PD.[46,47] Being a cytoplasmic soluble protein of about 14 kDa in healthy neurons in the CNS, α-synuclein functions predominantly in neuronal synapses under physiological conditions.[46,47] Although the full gamut of α-synuclein physiological functions remains to be elucidated, studies indicate that α-synuclein promotes the interactions between synaptic membrane proteins and SNARE complexes mediating the formation of synaptic vesicles of neurotransmitters, by assuming unfixed monomeric structures in the nerve terminals.[48,49] In addition, α-synuclein may also promote[50] and maintain the lipid bilayer structure,[51,52] and cause lipid membrane remodelling under different conditions.[53-55] In familial PD, however, α-synuclein is mutated, become aggregated and deposited,[56,57] and involved as a chief component in forming Lewy bodies.[58,59]Thus, α-synuclein forms an insoluble fibrous structure in PD with Lewy body dementia and multiple systemic sclerosis.[60,61]

How α-synuclein is assembled from soluble monomers in physiological status into fibrous structures of Lewy bodies under the pathological conditions remains elusive. Recent studies have demonstrated that acetylation of α-synuclein at the amino terminus results in a compact structure, preventing the non-β-amyloid aggregation domains from being exposure and thus precluding spontaneous aggregation.[62] When α-synuclein forms an insoluble fibrous structure, there are mutually overlapping β-sheets with a hydrophobic core and diverse complex configurations in its amyloid structure.[60] Each of these complexes consists of an intermolecular metal ion bridge, glutamine-bound ladders, and zipper-like structures to stabilize a predominantly β-sheet composed structure of orthorhombic Greek pattern.[60]

The metal ion bridge in this complex is of particular interest given the elevated levels of copper (Cu^{2+}) and manganese (Mn^{2+}) in PD settings. It has been demonstrated that Cu^{2+} binds directly to the amino terminus of α-synuclein, in which the His-50 amino acid residue is required as an anchoring position for Cu^{2+}.[63] In addition, the acidic carboxyl terminal region of α-synuclein[64,65] appears involved in α-synuclein oxidation and oligomer formation and in mediating a weakly bound second cation of Cu^{2+}.[63] Furthermore, the amino terminal acetylation of the His-50 residue or H50Q mutation has been shown to inhibit α-synuclein binding to Cu^{2+}.[66] Together these findings suggest that Cu^{2+} binding to α-synuclein mediates α-synuclein polymerization by forming intermolecular metal ion bridges.[60,63,66-68]

4 | THE ROLE OF MANGANESE (MN^{2+})

The trace metal Mn^{2+} is essential for 50%-70% of the enzymes in the body, including its participation in activation of glutamate synthase, arginase and manganese super (MnSOD or SOD2).[69,70] While this divalent cation metal is mainly distributed in the lysosome, Mn^{2+} is also at considerable levels in mitochondria, necessary for a variety of enzymes' activities.[71,72] Notably Mn^{2+} is a co-enzyme for mitochondrial type II superoxide dismutase (SOD2) activity, its distribution and metabolism must be strictly regulated, and deregulation of Mn^{2+} homeostasis can lead to the occurrence of various disease conditions.[73]

Excessive Mn^{2+} produces neurotoxicity in dopaminergic animal models and in cell cultures exposed to exogenous Mn^{2+}.[74-76] Chronic accumulation of excessive Mn^{2+} in the brain leads to irreversible neuropathy assembling PD.[77] By contrast, Mn^{2+} deficiency also causes

abnormal responses in the nervous system and animal behaviour, as well as abnormalities in bone development and other biochemical reactions.[78,79] Studies have confirmed that manganese ion is not only one of the pathogenic factors of PD,[80] but also involved in triggering degeneration in various nervous systems.[77] Recently, it has been shown that Mn^{2+} binds to α-synuclein and that expression of α-synuclein affects intracellular Mn^{2+} storage,[81] however increases in Mn^{2+} promote the aggregation of α-synuclein.[82,83] Thus, α-synuclein may serve not only as an effector of trace metals but also as a sensor for changes in Mn^{2+} concentrations, reflecting an important molecular interaction between α-synuclein and Mn^{2+} in PD pathophysiology. Mn^{2+} availability may therefore be critical to α-synuclein and excess Mn^{2+} may trigger α-synuclein insolubility (Figure 1).

5 | LYSOSOMAL HANDLING OF TRACE METALS AND LIPIDS

High intracellular Mn^{2+} content, which induces neuronal toxicity, may be caused by excessive entry into the cell by endocytosis, or reduced removal transport by exocytosis and vesicle recirculation. As the main storage of Mn^{2+} and center of intra- and extra-cellular transports, lysosomes are membranous organelles of 0.1 to 1.2 microns that play a key role in quality control of the cytoplasmic and organelle environmental homeostasis. Lysosomes regulate cellular micro-environmental homeostasis by trans-lysosomal membrane transports and fusion with other subcellular structures. Interestingly, while Mn^{2+} entry into and exit out of lysosomes require cross-membrane transport machineries, lysosomal Mn^{2+} is exported out of cells with vesicular fusions with plasma membrane, and while lysosomal Mn^{2+} is transported into the cytoplasm with concentration difference, Mn^{2+} is transported into lysosome from the cytoplasm by inverse concentration difference.[84-86]

Even though the molecular mechanism of lysosomal transport of metal ions remains largely to be investigated, studies have indicated that the by-membrane transport disorder of lysosomal homeostasis and the decrease in lysosome numbers are associated with dopaminergic neuronal degeneration in PD.[87] Lysosomal storage disorders (LSD) share a significant risk with the motor and cognitive disorders in PD. Such LSD as Gaucher disease (GD) and Niemann-Pick disease (NPC) that are lipid storage disorders show some common molecular pathologic abnormalities to that in PD, including Lewy body eosinophilic inclusions.[88-92] Mutations of *sphingomyelin phosphodiesterase 1* (*SMPD1*) or the cholesterol transporter *NPC1* genes constitute as significant risk factors of PD.[93,94] Moreover, the *SMPD1* gene product sphingomyelinase is stimulated by Mn^{2+} for activity.[95-97] It might be possible that lysosomal cross-membrane transport affects the structure and solubility of α-synuclein via disarrayed lipids and trace metals in affected neurons. The disordered molecular elements resulting from lysosomal dysfunction may thus significantly contribute to the formation of eosinophilic inclusions and degeneration of neuronal senescence.[87-89,93,94]

Furthermore, lysosomes play an obligatory role in autophagy that is required for compromised organelles including mitochondria to be recycled. Failure of mitochondrial maintenance and regulation is involved in PD pathogenesis.[98] Notably, ATP13A2 deficiency has been shown to contribute mitochondrial dysfunction[99-101] and one of the mechanisms in mediating mitochondrial dyshomeostasis is compromised autophagy.[102] ATP13A2 deficiency has been shown to be

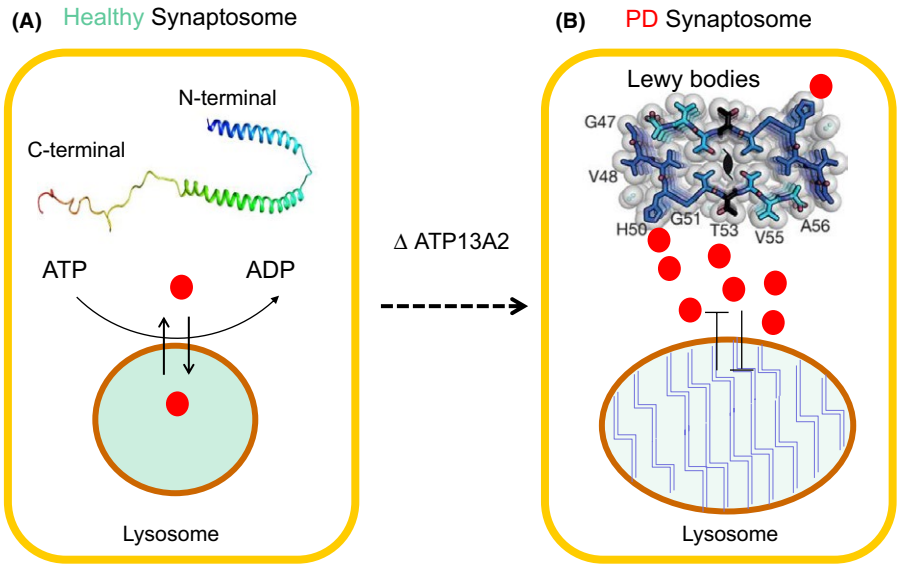

FIGURE 1 Schematic of α-synuclein aggregation incurred by metal trafficking disorder. α-synuclein aggregation may be triggered by a transport failure of ATP13A2 substrates from cytoplasm to lysosomes. The resultant cytoplasmic retention of toxic cation substrates may participate in synuclein aggregation and precipitation, causing neural cell loss of function and thus degeneration. Red circles depict trace metal cations, such as Cu^{2+} and Mn^{2+} that undergo constant equilibrium between cytoplasmic and lysosomal compartments, which is mediated by ATP13A2 hydrolysis of ATP to ADP under physiological conditions (A). When ATP13A2 function is lost, there becomes some cytoplasmic aberrant buildup of the metal cations and their associated molecules (B). The drawings of α-synuclein protein aggregate structures and amino acid residues are according to the publication Rodriguez JA et al. *Nature*, 2015;525:486-490

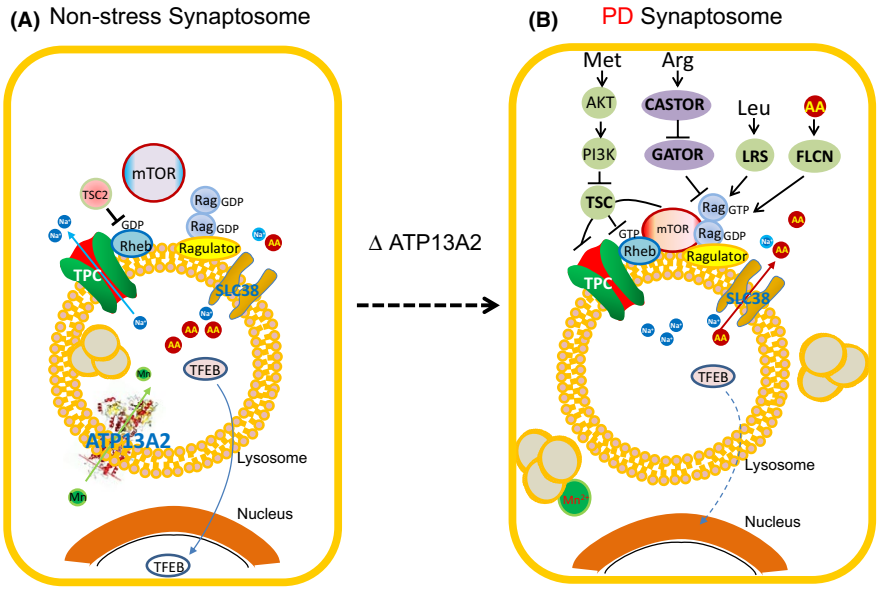

FIGURE 2 Lysosome integrations of cytoplasmic clearance of toxicity, stress-stimulated metabolisms and related gene expressions. Lysosomal membranes are equipped with various ATPase pumps, ion channels and amino acid channels, and are also bound by GTPases and their regulatory proteins. (A) Under non-stress conditions, TSC2 is involved in stimulating Rheb GTPase activity rendering Rheb in GDP-bound conformation, TPC pumps out Na^+, and ATP13A2 might pumps in Mn^{2+}, together in favor of mTOR inactivation. (B) When ATP13A2 becomes deficient as in PD conditions, TSC2 is ubiquitinated and degraded by proteasomes, rendering Rheb in GTP-bound confirmation, and SLC38 pumps out amino acids to activate Akt, CASTOR, LRS and FLCN, together resulting in mTOR activation in association with lysosomes and lysosomal transcription factor TFEB inhibition. Thus, lysosomal dysfunctions in trafficking and autophagy can be induced with lysosomal dyshomeostasis by ATP13A2 mutation-associated cross-membrane transport, TSC2 deficiency-induced mTOR activation and suppression of TFEB transcription factor-induced gene transcriptions for lysosomal proteins. Mn denotes manganese and AA denotes amino acids

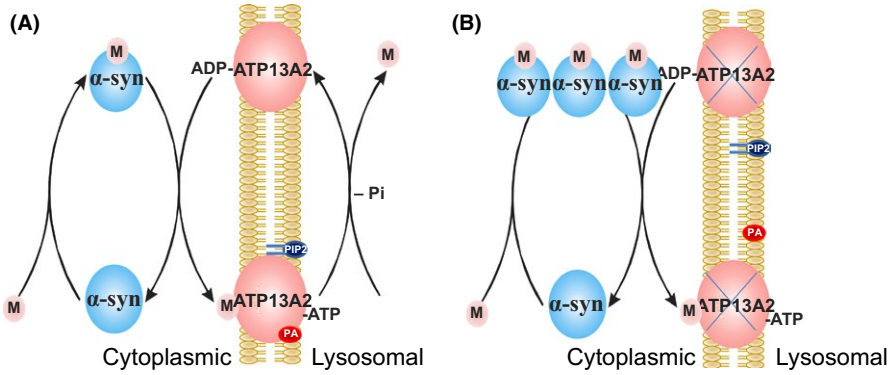

FIGURE 3 Model of α-synuclein mediation of trace metals to ATP13A2 for removal from cytoplasmic compartment into lysosomal compartments. (A) α-Synuclein binds trace metals and presents the cations to ADP-bound ATP13A2 stimulating ATP exchange for ADP and a structural conformational change. PA and PI(3,5)P2 stimulate ATP-bound ATP13A2 to hydrolyze ATP to ADP with further conformational changes moving bound metals across into lysosomes. (B) Loss of ATP13A2 function results in failure of ATP13A2 substrate transport into lysosomal compartments and cytoplasmic accumulations thereby mediating α-synuclein aggregations

associated with MYCBP2-induced ubiquitination of TSC2, leading to Rheb GTPase in a GTP-bound conformation and mTORC1 activation on lysosomes, thereby inhibition of TFEB-mediated lysosomal gene transcriptions and inhibition of autophagy[102] (Figure 2).

6 | *ATP13A2* GENE MUTATION

The *ATP13A2* gene is a recessive mutation disease-causing gene at chromosome 1p36 of early-onset young PD patients with dementia. It encodes 1180 amino acids and contains 10 hydrophobic transmembrane regions. ATP13A2 as a P-type transporter plays an important role in the regulation of Mn^{2+} homeostasis.[103] In PD patients, multiple ATP13A2 gene mutations have been identified.[104] In primary cultured rat neurons, the wild-type ATP13A2 protects the cells from the toxic effects of Mn^{2+} and reduces the release of cytochrome c from the mitochondria, but its pathogenic mutants have no such ability, suggesting that ATP13A2 is essential against Mn^{2+} cytotoxicity by regulating the cell Mn^{2+} homeostasis.[105] Knockdown of ATP13A2 expression in cultured neurons and cerebral cortical neurons results in

the generation of large amounts of ROS and mitochondrial dysfunction.[106] As a metal transporter, however, ATP13A2 corresponding specificity for trace metal ligand and its mechanisms of action have not been fully understood.[107]

In the yeast cell knockout of the *ypk9* gene (*ATP13A2* homologous gene), its growth was affected by particular metal ions, such as cadmium, selenium, manganese and nickel, which suggested that ATP13A2 is related to the transport of these ions.[108] Among them, Mn^{2+} ion is one of the most toxic trace elements that are known to be toxic to neurons.[108] Expression of ATP13A2 reduces the toxicity of Mn^{2+} to nerve cells.[105,109] In the *ATP13A2* gene knocked out mice, deficiency causes glial accumulations of ubiquitinated proteins, lipofuscinosis, and disorders of endocytic pathways, leading to age-related abnormal movements similar to PD.[110] Furthermore, *ATP13A2* gene mutation in PD has been shown to be associated with a wide range of lysosomal damages including defective lysosomal acidification, dysfunction of hydrolase processing and substrate degradation, decreased clearance of autophagosomes, andα-synuclein aggregation and cell death.[111] With these findings, it is possible that ATP13A2 failure in transport Mn^{2+} precipitates Lewy body formation in brain regions involved in not only motor but also behavioural deficits, by dysfunctional cross-membrane transport in the lysosomal compartments (Figure 1).

To date, little is known of the operative and regulatory mechanisms of ATP13A2. Recent studies show that α-synuclein aggregation is enhanced by ATP13A2 mutation.[112] With α-synuclein binding to Mn^{2+} and regulating Mn^{2+} storage, and ATP13A2 as a potential Mn^{2+} transporter, we hypothesize that α-synuclein presents Mn^{2+} or other metals such as Cu^{2+} to ATP13A2 for transport (Figure 3). Since ATP13A2 might interact with synaptotagmin-11 encoded by *SYT11* that is mutated in PD and regulates autophagy in the same pathway as ATP13A2,[102] and synaptotagmins bind a series of different cations,[113,114] it is also possible that synaptotagmin-11 regulates ATP13A2 transport efficiency. In addition, ATP13A2 contains a unique N-terminal hydrophobic extension on the lysosomal cytosolic membrane surface to interact with phosphatidic acid (PA) and phosphatidylinositol(3,5)bisphosphate [PI(3,5)P2] that stimulate ATP13A2 auto-phosphorylation[115] and are required for the ATP13A2-mediated protection against the toxic metals Mn^{2+}, Zn^{2+}, and Fe^{3+}[99] (Figure 3). ATP13A2 deficiency results in neuronal ceroid lipofuscinosis including accumulation of lipofuscin positive for subunit c of mitochondrial ATP synthase, suggesting that a common pathogenic mechanism underlies both neuronal ceroid lipofuscinosis and Parkinson's disease.[100] It is thus possible that ATP13A2 deficiency entrains dyshomeostasis of trace metals and lipids moieties between the sides of lysosomal membrane, regulated by proteins including α-synuclein and synaptotagmin-11. Further studies are required to delineate the natures of ATP13A2 transport and its importance in particular brain regions especially sensitive to lesions in Parkinsonism and ICD.

Taken together, cross-lysosomal membrane transport by ATP13A2 transporters is critical in the maintenance of proteostasis of sensing proteins such as α-synuclein and homeostasis of lysosomal compartments. Storage disorders on each side of the lysosomal membranes are triggered by gene mutations and deregulated expressions of ATP13A2, instigate trafficking disorders of α-synuclein aggregates and damaged organelles, including compromised mitophagy, in particular regions of CNS. Selective neuronal degeneration and aberrant transmission involving the OFC and corpus striatum circuits may thereby underpin PD ICD.

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REFERENCES

1. Potenza MN, Voon V, Weintraub D. Drug Insight: impulse control disorders and dopamine therapies in Parkinson's disease. *Nat Clin Pract Neurol*. 2007;3:664–672.
2. Carriere N, Lopes R, Defebvre L, Delmaire C, Dujardin K. Impaired corticostriatal connectivity in impulse control disorders in Parkinson disease. *Neurology*. 2015;84:2116–2123.
3. Weintraub D, David AS, Evans AH, Grant JE, Stacy M. Clinical spectrum of impulse control disorders in Parkinson's disease. *Mov Disord*. 2015;30:121–127.
4. Napier TC, Corvol JC, Grace AA, et al. Linking neuroscience with modern concepts of impulse control disorders in Parkinson's disease. *Mov Disord*. 2015;30:141–149.
5. Steinberg L, Chein JM. Multiple accounts of adolescent impulsivity. *Proc Natl Acad Sci U S A*. 2015;112:8807–8808.
6. Papay K, Mamikonyan E, Siderowf AD, et al. Patient versus informant reporting of ICD symptoms in Parkinson's disease using the QUIP: validity and variability. *Parkinsonism Relat Disord*. 2011;17:153–155.
7. Djamshidian A, O'Sullivan SS, Sanotsky Y, et al. Decision making, impulsivity, and addictions: do Parkinson's disease patients jump to conclusions? *Mov Disord*. 2012;27:1137–1145.
8. Joutsa J, Martikainen K, Vahlberg T, Voon V, Kaasinen V. Impulse control disorders and depression in Finnish patients with Parkinson's disease. *Parkinsonism Relat Disord*. 2012;18:155–160.
9. Voon V, Hassan K, Zurowski M, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. *Neurology*. 2006;67:1254–1257.
10. Potenza MN, Koran LM, Pallanti S. The relationship between impulse-control disorders and obsessive-compulsive disorder: a current understanding and future research directions. *Psychiatry Res*. 2009;170:22–31.
11. Stein DJ, Grant JE, Franklin ME, et al. Trichotillomania (hair pulling disorder), skin picking disorder, and stereotypic movement disorder: toward DSM-V. *Depress Anxiety*. 2010;27:611–626.
12. Lochner C, Grant JE, Odlaug BL, Woods DW, Keuthen NJ, Stein DJ. DSM-5 field survey: hair-pulling disorder (trichotillomania). *Depress Anxiety*. 2012;29:1025–1031.
13. Odlaug BL, Lust K, Schreiber LR, et al. Compulsive sexual behavior in young adults. *Ann Clin Psychiatry*. 2013;25:193–200.
14. Grant JE, Atmaca M, Fineberg NA, et al. Impulse control disorders and "behavioural addictions" in the ICD-11. *World Psychiatry*. 2014;13:125–127.
15. Vallelunga A, Flaibani R, Formento-Dojot P, Biundo R, Facchini S, Antonini A. Role of genetic polymorphisms of the dopaminergic

system in Parkinson's disease patients with impulse control disorders. *Parkinsonism Relat Disord*. 2012;18:397–399.
16. Sharma A, Goyal V, Behari M, Srivastva A, Shukla G, Vibha D. Impulse control disorders and related behaviours (ICD-RBs) in Parkinson's disease patients: assessment using "Questionnaire for impulsive-compulsive disorders in Parkinson's disease" (QUIP). *Ann Indian Acad Neurol*. 2015;18:49–59.
17. Poletti M, Lucetti C, Baldacci F, Del Dotto P, Bonuccelli U. Concomitant development of hypersexuality and delusional jealousy in patients with Parkinson's disease: a case series. *Parkinsonism Relat Disord*. 2014;20:1290–1292.
18. Perez-Lloret S, Rey MV, Fabre N, et al. Prevalence and pharmacological factors associated with impulse-control disorder symptoms in patients with Parkinson disease. *Clin Neuropharmacol*. 2012;35:261–265.
19. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol*. 2010;67:589–595.
20. Weintraub D, Siderowf AD, Potenza MN, et al. Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Arch Neurol*. 2006;63:969–973.
21. Muller A, Rein K, Kollei I, et al. Impulse control disorders in psychiatric inpatients. *Psychiatry Res*. 2011;188:434–438.
22. Odlaug BL, Grant JE. Impulse-control disorders in a college sample: results from the self-administered Minnesota Impulse Disorders Interview (MIDI). *Prim Care Companion J Clin Psychiatry*. 2010;12: DOI: 10.4088/PCC.09m00842whi.
23. Tse W, Halbig TD. Skin picking in Parkinson's disease: a behavioral side-effect of dopaminergic treatment? *Psychiatry Clin Neurosci*. 2010;64:214.
24. Grant JE, Odlaug BL, Chamberlain SR. A cognitive comparison of pathological skin picking and trichotillomania. *J Psychiatr Res*. 2011;45:1634–1638.
25. Muller T, Haas T, Lutge S, Marg M, Ehret R. Trichophagia affects response to duodenal levodopa/carbidopa gel administration. *Mov Disord*. 2012;27:588–590.
26. Weintraub D, Simuni T, Caspell-Garcia C, et al. Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. *Mov Disord*. 2015;30:919–927.
27. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev*. 2008;32:525–549.
28. Harrison BJ, Soriano-Mas C, Pujol J, et al. Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2009;66:1189–1200.
29. Rao H, Mamikonyan E, Detre JA, et al. Decreased ventral striatal activity with impulse control disorders in Parkinson's disease. *Mov Disord*. 2010;25:1660–1669.
30. van den Bos W, Rodriguez CA, Schweitzer JB, McClure SM. Adolescent impatience decreases with increased frontostriatal connectivity. *Proc Natl Acad Sci U S A*. 2015;112:E3765–E3774.
31. Casey B, Jones RM, Somerville LH. Braking and accelerating of the adolescent brain. *J Res Adolesc*. 2011;21:21–33.
32. Fineberg NA, Potenza MN, Chamberlain SR, et al. Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. *Neuropsychopharmacology*. 2010;35:591–604.
33. Roberts AC. The importance of serotonin for orbitofrontal function. *Biol Psychiatry*. 2011;69:1185–1191.
34. Chamberlain SR, Menzies L, Hampshire A, et al. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. *Science*. 2008;321:421–422.
35. Graybiel AM, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. *Neuron*. 2000;28:343–347.
36. Aouizerate B, Guehl D, Cuny E, et al. Pathophysiology of obsessive-compulsive disorder: a necessary link between phenomenology, neuropsychology, imagery and physiology. *Prog Neurobiol*. 2004;72:195–221.
37. Zainal Abidin S, Tan EL, Chan SC, et al. DRD and GRIN2B polymorphisms and their association with the development of impulse control behaviour among Malaysian Parkinson's disease patients. *BMC Neurol*. 2015;15:59. DOI: 10.1186/s12883-015-0316-2.
38. Payer DE, Guttman M, Kish SJ, et al. [(1)(1)C]-(+)-PHNO PET imaging of dopamine D(2/3) receptors in Parkinson's disease with impulse control disorders. *Mov Disord*. 2015;30:160–166.
39. Wu K, Politis M, O'Sullivan SS, et al. Single versus multiple impulse control disorders in Parkinson's disease: an (1)(1)C-raclopride positron emission tomography study of reward cue-evoked striatal dopamine release. *J Neurol*. 2015;262:1504–1514.
40. Coccaro EF, McCloskey MS, Fitzgerald DA, Phan KL. Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. *Biol Psychiatry*. 2007;62:168–178.
41. Hamann S, Herman RA, Nolan CL, Wallen K. Men and women differ in amygdala response to visual sexual stimuli. *Nature Neurosci*. 2004;7:411–416.
42. Klavir O, Genud-Gabai R, Paz R. Functional connectivity between amygdala and cingulate cortex for adaptive aversive learning. *Neuron*. 2013;80:1290–1300.
43. Hong W, Kim DW, Anderson DJ. Antagonistic control of social versus repetitive self-grooming behaviors by separable amygdala neuronal subsets. *Cell*. 2014;158:1348–1361.
44. Via E, Cardoner N, Pujol J, et al. Amygdala activation and symptom dimensions in obsessive-compulsive disorder. *Br J Psychiatry*. 2014;204:61–68.
45. Adhikari A, Lerner TN, Finkelstein J, et al. Basomedial amygdala mediates top-down control of anxiety and fear. *Nature*. 2015;527:179–185.
46. Maroteaux L, Campanelli JT, Scheller RH. Synuclein: a neuron-specific protein localized to the nucleus and presynaptic nerve terminal. *J Neurosci*. 1988;8:2804–2815.
47. Iwai A, Masliah E, Yoshimoto M, et al. The precursor protein of non-A beta component of Alzheimer's disease amyloid is a presynaptic protein of the central nervous system. *Neuron*. 1995;14:467–475.
48. Burre J, Sharma M, Sudhof TC. Alpha-synuclein assembles into higher-order multimers upon membrane binding to promote SNARE complex formation. *Proc Natl Acad Sci U S A*. 2014;111:E4274–E4283.
49. Burre J, Sharma M, Tsetsenis T, Buchman V, Etherton MR, Sudhof TC. Alpha-synuclein promotes SNARE-complex assembly in vivo and in vitro. *Science*. 2010;329:1663–1667.
50. Ouberai MM, Wang J, Swann MJ, et al. Alpha-synuclein senses lipid packing defects and induces lateral expansion of lipids leading to membrane remodeling. *J Biol Chem*. 2013;288:20883–20895.
51. Galvagnion C, Brown JW, Ouberai MM, et al. Chemical properties of lipids strongly affect the kinetics of the membrane-induced aggregation of alpha-synuclein. *Proc Natl Acad Sci U S A*. 2016;113:7065–7070.
52. Braun AR, Sevcsik E, Chin P, Rhoades E, Tristram-Nagle S, Sachs JN. Alpha-synuclein induces both positive mean curvature and negative Gaussian curvature in membranes. *J Am Chem Soc*. 2012;134:2613–2620.
53. Braun AR, Lacy MM, Ducas VC, Rhoades E, Sachs JN. Alpha-synuclein-induced membrane remodeling is driven by binding affinity, partition depth, and interleaflet order asymmetry. *J Am Chem Soc*. 2014;136:9962–9972.
54. Varkey J, Isas JM, Mizuno N, et al. Membrane curvature induction and tubulation are common features of synucleins and apolipoproteins. *J Biol Chem*. 2010;285:32486–32493.
55. Braun AR, Sachs JN. Alpha-synuclein reduces tension and increases undulations in simulations of small unilamellar vesicles. *Biophys J*. 2015;108:1848–1851.

56. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science*. 1997;276:2045–2047.
57. Conway KA, Harper JD, Lansbury PT. Accelerated in vitro fibril formation by a mutant alpha-synuclein linked to early-onset Parkinson disease. *Nat Med*. 1998;4:1318–1320.
58. Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M. Alpha-synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proc Natl Acad Sci U S A*. 1998;95:6469–6473.
59. Baba M, Nakajo S, Tu PH, et al. Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. *Am J Pathol*. 1998;152:879–884.
60. Tuttle MD, Comellas G, Nieuwkoop AJ, et al. Solid-state NMR structure of a pathogenic fibril of full-length human alpha-synuclein. *Nat Struct Molec Biol*. 2016;23:409–415.
61. Bras J, Guerreiro R, Darwent L, et al. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. *Hum Mol Genet*. 2014;23:6139–6146.
62. Theillet FX, Binolfi A, Bekei B, et al. Structural disorder of monomeric alpha-synuclein persists in mammalian cells. *Nature*. 2016;530:45–50.
63. Rasia RM, Bertoncini CW, Marsh D, et al. Structural characterization of copper(II) binding to alpha-synuclein: Insights into the bioinorganic chemistry of Parkinson's disease. *Proc Natl Acad Sci U S A*. 2005;102:4294–4299.
64. Paik SR, Shin HJ, Lee JH. Metal-catalyzed oxidation of alpha-synuclein in the presence of Copper(II) and hydrogen peroxide. *Arch Biochem Biophys*. 2000;378:269–277.
65. Lee EN, Lee SY, Lee D, Kim J, Paik SR. Lipid interaction of alpha-synuclein during the metal-catalyzed oxidation in the presence of Cu^{2+} and H_2O_2. *J Neurochem*. 2003;84:1128–1142.
66. Mason RJ, Paskins AR, Dalton CF, Smith DP. Copper binding and subsequent aggregation of alpha-synuclein are modulated by N-terminal acetylation and ablated by the H50Q missense mutation. *Biochemistry*. 2016; DOI: 10.1021/acs.biochem.6b00708.
67. Moriarty GM, Minetti CA, Remeta DP, Baum J. A revised picture of the Cu(II)-alpha-synuclein complex: the role of N-terminal acetylation. *Biochemistry*. 2014;53:2815–2817.
68. Miotto MC, Valiente-Gabioud AA, Rossetti G, et al. Copper binding to the N-terminally acetylated, naturally occurring form of alpha-synuclein induces local helical folding. *J Am Chem Soc*. 2015;137:6444–6447.
69. Carl GF, Blackwell LK, Barnett FC, et al. Manganese and epilepsy: brain glutamine synthetase and liver arginase activities in genetically epilepsy prone and chronically seizured rats. *Epilepsia*. 1993;34:441–446.
70. Takeda A. Manganese action in brain function. *Brain Res Brain Res Rev*. 2003;41:79–87.
71. Fitsanakis VA, Zhang N, Garcia S, Aschner M. Manganese (Mn) and iron (Fe): interdependency of transport and regulation. *Neurotox Res*. 2010;18:124–131.
72. Au C, Benedetto A, Aschner M. Manganese transport in eukaryotes: the role of DMT1. *Neurotoxicology*. 2008;29:569–576.
73. Ljung K, Vahter M. Time to re-evaluate the guideline value for manganese in drinking water? *Environ Health Perspect*. 2007;115:1533–1538.
74. Aschner M, Erikson KM, Dorman DC. Manganese dosimetry: species differences and implications for neurotoxicity. *Crit Rev Toxicol*. 2005;35:1–32.
75. Latchoumycandane C, Anantharam V, Kitazawa M, Yang Y, Kanthasamy A, Kanthasamy AG. Protein kinase Cdelta is a key downstream mediator of manganese-induced apoptosis in dopaminergic neuronal cells. *J Pharmacol Exp Ther*. 2005;313:46–55.
76. Zhang D, Kanthasamy A, Anantharam V. Effects of manganese on tyrosine hydroxylase (TH) activity and TH-phosphorylation in a dopaminergic neural cell line. *Toxicol Appl Pharmacol*. 2011;254:65–71.
77. Mergler D, Baldwin M, Belanger S, et al. Manganese neurotoxicity, a continuum of dysfunction: results from a community based study. *Neurotoxicology*. 1999;20:327–342.
78. Hurley LS. Teratogenic aspects of manganese, zinc, and copper nutrition. *Physiol Rev*. 1981;61:249–295.
79. Strause L, Saltman P, Glowacki J. The effect of deficiencies of manganese and copper on osteoinduction and on resorption of bone particles in rats. *Calcif Tissue Int*. 1987;41:145–150.
80. Kim Y, Kim JM, Kim JW, et al. Dopamine transporter density is decreased in parkinsonian patients with a history of manganese exposure: what does it mean? *Mov Disord*. 2002;17:568–575.
81. Ducic T, Carboni E, Lai B, et al. Alpha-synuclein regulates neuronal levels of manganese and calcium. *ACS Chem Neurosci*. 2015;6:1769–1779.
82. Jinsmaa Y, Sullivan P, Gross D, Cooney A, Sharabi Y, Goldstein DS. Divalent metal ions enhance DOPAL-induced oligomerization of alpha-synuclein. *Neurosci Lett*. 2014;569:27–32.
83. Harischandra DS, Jin H, Anantharam V, Kanthasamy A, Kanthasamy AG. Alpha-synuclein protects against manganese neurotoxic insult during the early stages of exposure in a dopaminergic cell model of Parkinson's disease. *Toxicol Sci*. 2015;143:454–468.
84. Bogunovic B, Stojakovic M, Chen L, Maric M. An unexpected functional link between lysosomal thiol reductase and mitochondrial manganese superoxide dismutase. *J Biol Chem*. 2008;283:8855–8862.
85. Gorojod RM, Alaimo A, Porte Alcon S, Pomilio C, Saravia F, Kotler ML. The autophagic- lysosomal pathway determines the fate of glial cells under manganese- induced oxidative stress conditions. *Free Radic Biol Med*. 2015;87:237–251.
86. Okamoto Y, Oshima R, Inagaki K, et al. The presence of a manganese-rich particle in lysosome of rat pancreas due to excess manganese treatment. *Biochem Mol Biol Int*. 1997;41:389–394.
87. Dehay B, Bove J, Rodriguez-Muela N, et al. Pathogenic lysosomal depletion in Parkinson's disease. *J Neurosci*. 2010;30:12535–12544.
88. Mazzulli JR, Zunke F, Tsunemi T, et al. Activation of beta-glucocerebrosidase reduces pathological alpha-synuclein and restores lysosomal function in Parkinson's patient midbrain neurons. *J Neurosci*. 2016;36:7693–7706.
89. Mazzulli JR, Xu YH, Sun Y, et al. Gaucher disease glucocerebrosidase and alpha-synuclein form a bidirectional pathogenic loop in synucleinopathies. *Cell*. 2011;146:37–52.
90. Liu JP. New functions of cholesterol binding proteins. *Mol Cell Endocrinol*. 2009;303:1–6.
91. Liu JP, Tang Y, Zhou S, Toh BH, McLean C, Li H. Cholesterol involvement in the pathogenesis of neurodegenerative diseases. *Mol Cell Neurosci*. 2009;43:33–42.
92. Tang Y, Li H, Liu JP. Niemann-Pick disease type C: from molecule to clinic. *Clin Exp Pharmacol Physiol*. 2010;37:132–140.
93. Gan-Or Z, Ozelius LJ, Bar-Shira A, et al. The p. L302P mutation in the lysosomal enzyme gene SMPD1 is a risk factor for Parkinson disease. *Neurology*. 2013;80:1606–1610.
94. Kluenemann HH, Nutt JG, Davis MY, Bird TD. Parkinsonism syndrome in heterozygotes for Niemann-Pick C1. *J Neurol Sci*. 2013;335:219–220.
95. Carre JB, Morand O, Homayoun P, Roux F, Bourre JM, Baumann N. Purified rat brain microvessels exhibit both acid and neutral sphingomyelinase activities. *J Neurochem*. 1989;52:1294–1299.
96. Ella KM, Qi C, Dolan JW, Thompson RP, Meier KE. Characterization of a sphingomyelinase activity in *Saccharomyces cerevisiae*. *Arch Biochem Biophys*. 1997;340:101–110.
97. Raimann PE, Custodio de Souza IC, Bernard EA, Guma FC. An Mn^{2+}-stimulated neutral-sphingomyelinase in seminiferous tubules of immature Wistar rats. *Mol Cell Biochem*. 1999;201:125–129.

98. Liu JP. Molecular mechanisms of ageing and related diseases. *Clin Exp Pharmacol Physiol*. 2014;41:445–458.
99. Martin S, van Veen S, Holemans T, et al. Protection against mitochondrial and metal toxicity depends on functional lipid binding sites in ATP13A2. *Parkinsons Dis*. 2016;2016:9531917.
100. Sato S, Koike M, Funayama M, et al. Lysosomal storage of subunit c of mitochondrial ATP synthase in brain-specific Atp13a2-deficient mice. *Am J Pathol*. 2016; DOI: 10.1016/j.ajpath.2016.08.006.
101. Park JS, Koentjoro B, Veivers D, Mackay-Sim A, Sue CM. Parkinson's disease-associated human ATP13A2 (PARK9) deficiency causes zinc dyshomeostasis and mitochondrial dysfunction. *Hum Mol Genet*. 2014;23:2802–2815.
102. Bento CF, Ashkenazi A, Jimenez-Sanchez M, Rubinsztein DC. The Parkinson's disease-associated genes ATP13A2 and SYT11 regulate autophagy via a common pathway. *Nat Commun*. 2016;7:11803.
103. Kwasnicka-Crawford DA, Carson AR, Roberts W, et al. Characterization of a novel cation transporter ATPase gene (ATP13A4) interrupted by 3q25-q29 inversion in an individual with language delay. *Genomics*. 2005;86:182–194.
104. Ning YP, Kanai K, Tomiyama H, et al. PARK9-linked parkinsonism in eastern Asia: mutation detection in ATP13A2 and clinical phenotype. *Neurology*. 2008;70:1491–1493.
105. Tan J, Zhang T, Jiang L, et al. Regulation of intracellular manganese homeostasis by Kufor-Rakeb syndrome-associated ATP13A2 protein. *J Biol Chem*. 2011;286:29654–29662.
106. Gusdon AM, Zhu J, Van Houten B, Chu CT. ATP13A2 regulates mitochondrial bioenergetics through macroautophagy. *Neurobiol Dis*. 2012;45:962–972.
107. Ramonet D, Podhajska A, Stafa K, et al. PARK9-associated ATP13A2 localizes to intracellular acidic vesicles and regulates cation homeostasis and neuronal integrity. *Hum Mol Genet*. 2012;21:1725–1743.
108. Schmidt K, Wolfe DM, Stiller B, Pearce DA. Cd^{2+}, Mn^{2+}, Ni^{2+} and Se^{2+} toxicity to *Saccharomyces cerevisiae* lacking YPK9p the orthologue of human ATP13A2. *Biochem Biophys Res Commun*. 2009;383:198–202.
109. Gitler AD, Chesi A, Geddie ML, et al. Alpha-synuclein is part of a diverse and highly conserved interaction network that includes PARK9 and manganese toxicity. *Nat Genet*. 2009;41:308–315.
110. Kett LR, Stiller B, Bernath MM, et al. Alpha-synuclein-independent histopathological and motor deficits in mice lacking the endolysosomal Parkinsonism protein Atp13a2. *J Neurosci*. 2015;35:5724–5742.
111. Dehay B, Martinez-Vicente M, Caldwell GA, et al. Lysosomal impairment in Parkinson's disease. *Mov Disord*. 2013;28:725–732.
112. Lopes da Fonseca T, Pinho R, Outeiro TF. A familial ATP13A2 mutation enhances alpha-synuclein aggregation and promotes cell death. *Hum Mol Genet*. 2016; DOI: 10.1093/hmg/ddw147.
113. Bhalla A, Tucker WC, Chapman ER. Synaptotagmin isoforms couple distinct ranges of Ca^{2+}, Ba^{2+}, and Sr^{2+} concentration to SNARE-mediated membrane fusion. *Mol Biol Cell*. 2005;16:4755–4764.
114. Garcia RA, Godwin HA. High metal concentrations are required for self-association of synaptotagmin II. *Biophys J*. 2004;86:2455–2466.
115. Holemans T, Sorensen DM, van Veen S, et al. A lipid switch unlocks Parkinson's disease-associated ATP13A2. *Proc Natl Acad Sci U S A*. 2015;112:9040–9045.

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