Is Attention-Deficit/Hyperactivity Disorder a Risk Syndrome for Parkinson's Disease?

Alan A. Baumeister, PhD

Abstract: Recent epidemiological evidence indicates that diagnosis of attention-deficit/hyperactivity disorder (ADHD) is associated with increased risk for diseases of the basal ganglia and cerebellum, including Parkinson's disease (PD). The evidence reviewed here indicates that deficits in striatal dopamine are a shared component of the causal chains that produce these disorders. Neuropsychological studies of adult ADHD, prodromal PD, and early-stage PD reveal similar deficits in executive functions, memory, attention, and inhibition that are mediated by similar neural substrates. These and other findings are consistent with the possibility that ADHD may be part of the PD prodrome. The mechanisms that may mediate the association between PD and ADHD include neurotoxic effects of stimulants, other environmental exposures, and Lewy pathology. Understanding the nature of the association between PD and ADHD may provide insight into the etiology and pathogenesis of both disorders. The possible contribution of stimulants to this association may have important clinical and public health implications.

Keywords: amphetamine, attention-deficit/hyperactivity disorder, methylphenidate, Parkinson's disease, stimulants

The possible association between Parkinson's disease (PD) and attention-deficit/hyperactivity disorder (ADHD) is an important, newly emerging topic of inquiry. The possibility that PD and ADHD are related clinical entities has been suspected for at least 20 years. Until recently, the reasons for this suspicion were conjectural, resting primarily on putative common abnormalities of dopamine (DA) function. In what appears to be the first direct test of this hypothesis, Walitza and colleagues[1] sought to determine retrospectively whether patients with Parkinson's disease were more likely than controls to have had childhood onset ADHD. Although total scores on measures used to diagnose ADHD retrospectively were insufficient for such diagnosis, subjects with PD had significantly more core symptoms of ADHD in childhood.

A recent large-scale, retrospective, population-based cohort study of persons born in Utah between 1950 and 1992 provides additional evidence for a link between PD and ADHD.[2] In that study, to enhance diagnostic sensitivity, investigators used an outcome measure that included PD and related disorders (secondary PD, other degenerative diseases of the basal ganglia, and essential tremor), which they referred to collectively as diseases of the basal ganglia and cerebellum (BG&C). Risk for BG&C in a cohort of ~32,000 patients who had been diagnosed with ADHD was significantly increased 2.4-fold compared to ~159,000 matched non-ADHD controls. A comparable significant 2.6-fold increase in risk was also observed in ADHD patients when the outcome diagnosis was restricted to PD per se. Of particular note, the risk for BG&C was dramatically increased (6- to 8-fold) in persons with ADHD who were known to have been prescribed stimulant medication. By way of comparison, the risk for lung cancer among former heavy smokers with five or fewer years since quitting is increased 12-fold.[3] Thus, the magnitude of the reported association between BG&C and stimulant-treated ADHD is substantial.

These findings and others discussed below suggest that an important association exists between PD and ADHD. ADHD precedes PD by definition, if not in fact.[4] Thus, ADHD or factors associated with ADHD may be antecedents that increase the likelihood for subsequent development of PD. The delineation of such antecedents could have important implications for understanding the etiology and pathogenesis of both disorders. In the review that follows, evidence pertaining to the possible nature of the relationship between PD and ADHD is explored. First, an overview of PD is given to provide background for subsequent discussion.

OVERVIEW OF PARKINSON'S DISEASE

After Alzheimer's disease, PD is the next most common degenerative neurological disorder of senescence.[5–11] The incidence and prevalence of Parkinson's disease increase almost exponentially with age, affecting approximately 1% of persons over 60. PD occurs slightly more often in men than women, in a ratio of about 3 to 2. PD is the fastest-growing neurological disorder globally. The number of persons worldwide with PD doubled between 1990 and 2015. This increase

From the Department of Psychology, Louisiana State University.

Original manuscript received 11 April 2020; revised manuscript received 11 August 2020, accepted for publication subject to revision 18 September 2020; revised manuscript received 3 October 2020.

Correspondence: Alan A. Baumeister, PhD, Department of Psychology, 236 Audubon Hall, Louisiana State University, Baton Rouge, Louisiana 70805. Email: abaumei@lsu.edu

DOI: 10.1097/HRP.0000000000000283

is largely, but not wholly, explained by increased life expectancy and the consequent increased number of persons aged 60 and over.

The pathogenic mechanisms responsible for PD are manifold, interactive, complex, and elusive. Traditionally, PD has been divided into familial (inherited) and nonfamilial (sporadic) forms. The familial form accounts for a small subset (5%–10%) of total PD cases, most having early onset.[12] The sporadic form comprises the majority of senescent cases and has a strong environmental component.[13] It has recently become clear, however, that sporadic PD also has a heritable component.[14,15] Generally speaking, the clinical presentation and underlying pathology of familial and sporadic forms are similar.[16,17] These findings indicate that PD has multiple genetic and environmental causal pathways that converge on a common neurobiological substrate.[17,18]

The discovery in the 1980s of a neurotoxin called MPTP, which produces rapid and permanent parkinsonism in humans and animals, spurred intense interest in the role of environmental toxins.[19,20] Numerous potential environmental risk factors are associated with PD, including exposure to pesticides, herbicides, industrial solvents, and heavy metals, as well as rural living and farming/agriculture.[21,22] Such factors, however, individually account for only a small amount of the variance in PD. By contrast, smoking is associated with a 40% decrease in the risk for PD. It is not known whether the association between smoking and PD is causal. If so, reduced tobacco use resulting from public health initiatives may contribute to increasing rates of PD.[9]

Diagnosis of Parkinson's disease is usually based on clinical presentation of motor signs. Widely used diagnostic criteria require the occurrence of two or more of the following: resting tremor, bradykinesia, rigidity, and postural/gait instability. Clinical diagnosis can be confirmed only by postmortem neuropathologic analysis (see below). Clinical-pathological studies indicate that the accuracy of clinical diagnosis is ~50% and ~80% in patients with a disease duration of <5 years and >5 years, respectively.[23,24] Although motor signs are the principal clinical criteria for diagnosis of PD, a variety of nonmotor signs and symptoms also occur. These include REM sleep behavior disorder (e.g., dream enacting behavior), altered olfaction (e.g., hyposmia), gastrointestinal disorders (e.g., constipation), excessive daytime sleepiness, cognitive impairment, and depression.[25–27]

An important recent development in the diagnosis of PD is the recognition of a prodromal syndrome. The underlying pathology in PD develops slowly over many years, probably decades. A problem with using classic motor signs to diagnose PD is that these signs do not manifest until extensive neurodegeneration has occurred. Early identification of persons at risk for PD has potential therapeutic implications.[27] Prodromal PD syndrome is a heterogenous collection of subtle motor and nonmotor signs and symptoms. Subtle motor deficits are detectable on neuropsychological tests (e.g., Purdue Pegboard Test) several years before diagnosis of PD.[28] The nonmotor features of prodromal PD include constipation, hyposmia, and REM sleep behavior disorder. This sleep disorder is an especially powerful predictor of subsequent development of neurodegenerative disease, including PD, and precedes onset of PD by an average of 28 years.[29,30] Constipation is a risk factor for PD, and it may precede the onset of motor symptoms by as much as 20 years.[31–33] Olfactory dysfunction occurs in ~90% of patients with PD and is associated with increased risk for PD for up to 4 years before the motor signs emerge.[34] Other risk factors for PD include cognitive impairments, anxiety, and depression.[26,35,36]

The relationship between the premotor features of PD and its pathogenesis is of considerable interest. Neuronal inclusions, called Lewy bodies and Lewy neurites—consisting mostly of misfolded α-synuclein protein—are a pathologic hallmark of idiopathic PD.[37–40] According to Braak's hypothesis, PD is initiated by an unknown pathogen (e.g., a virus) that enters the body by way of the nasal cavity and gut, initiating Lewy pathology and producing the prodromal gastrointestinal and olfactory defects.[41–45] The pathology then spreads toward the central nervous system by way of olfactory and vagus nerves and enters the brain at the olfactory bulb and the dorsal motor nucleus of the vagus nerve. The rostral progression of pathology from the dorsal motor nucleus through the midbrain and forebrain eventually damages neural structures that control movement. Braak's hypothesis has considerable support.[46–49] Not all patients with PD, however, evidence the proposed pathologic changes in the proposed sequence, and the role of Lewy pathology in neurodegeneration is uncertain. It is not clear whether Lewy pathology is the cause of neurodegeneration or whether it is a neuroprotective response to neurodegeneration.[50–52] Either way, Lewy pathology is a biomarker for PD.

The pathognomonic feature of PD is selective degeneration of mesencephalic DA neurons.[53] For unknown reasons, DA neurons in the substantia nigra (SN) are more vulnerable than other DA pathways, including those in the adjacent ventral tegmental area (VTA). Postmortem histologic studies show that ~80% of SN and ~50% of VTA cell bodies are lost in advanced disease.[54,55] The heightened vulnerability of SN DA neurons may be related to differential cellular response to α-synuclein. Overexpression of a mutant α-synuclein gene in mice induces in vivo increases in firing rates of SN DA but not VTA DA neurons.[56] Moreover, mutant α-synuclein–induced activation of DA neurons occurred in middle-aged but not young adult mice. It was suggested that acquired sensitivity to this effect of α-synuclein may be an early pathophysiological marker of SN DA neuronal vulnerability that precedes neurodegeneration.

ADHD AND PD: A COMMON PATHWAY LINKAGE

Multiple lines of evidence suggest that PD and ADHD share structural, chemical, and functional alterations of mesencephalic DA neurons. Transcranial sonography (TCS) of the SN shows increased echogenicity, relative to control subjects,

in patients with PD[57–60] and in children and adolescents with ADHD.[61,62] In PD, hyperechogenicity of the SN, defined as greater than the 90th percentile of controls, is associated with a 17-fold increased risk for subsequent development of PD.[58] SN echogenicity is also increased in patients with neuroleptic-induced parkinsonism, and the size of the echogenic signal correlates with severity of parkinsonian symptoms.[63] In ADHD, SN hyperechogenicity has been reported in 48% of children and adolescents with ADHD, and size of the echogenic signal correlated positively with the severity of core symptoms of ADHD.[61] The methodologic quality of studies that have employed transcranial sonography in the diagnosis of PD is good. A meta-analysis of these studies[59] found that 26 of the 31 studies examined had a score of 10 or greater (out of a maximum of 14) on the Quality Assessment of Diagnostic Accuracy Studies.[64,65] In the two studies that found hyperechogenicity in persons with ADHD, one[62] employed a blinded design, the other[61] did not, and in both studies ADHD subjects received stimulant medication. Additional studies are needed to replicate transcranial sonography findings in children and adolescents with ADHD to determine whether SN hyperechogenicity occurs in adults with ADHD and to determine the role of stimulant medications on observed effects. Studies are also needed to determine the pathologic changes responsible for hyperechogenicity of the SN. Increased SN echogenicity in PD is associated with several pathologic changes, including gliosis and increased iron concentration.[59] Interestingly, a recent study found increased iron concentration in the striatum of adults with ADHD.[66] Additional studies are needed to determine whether iron is increased in the SN in ADHD, and whether SN hyperechogenicity is associated with alterations of nigrostriatal DA neurons.

PD and ADHD also have similar structural changes in projection regions of mesencephalic DA neurons. DA neurons of the SN project to the dorsal striatum (putamen and caudate). The DA pathway from the SN to the putamen is the first to lose neurons in PD, and it is thought to be primarily responsible for bradykinesia and rigidity.[67–69] Atrophy of the putamen is a common finding in structural MRI imaging of PD.[70] Scores of structural MRI studies of children and adults with ADHD have been conducted in the last 20 years, and multiple meta-analyses of these studies have been published.[71–74] A robust finding from these studies is reduced volume of the caudate and lentiform nuclei (i.e., the putamen and globus pallidus) in children with ADHD.

A caveat is warranted regarding structural changes in the striatum in ADHD. Several studies have found that reduced striatal volume detected by MRI in ADHD patients diminishes with age, to the extent that it is no longer detectable in adults.[72,73,75] This suggests that striatal development is delayed in ADHD but eventually normalizes in early adulthood. However, not all studies are in agreement in this regard. Using a relatively large sample and conventional T1-weighted imaging, Proal and colleagues[76] found significantly reduced caudate volume in adults with ADHD. Moreover, a recent study by Sethi and colleagues[66] indicates that conventional MRI has reduced sensitivity to detect striatal abnormalities in adults with ADHD. In this study, magnetization transfer imaging (MTI), which provides improved contrast between white and gray matter, detected reduced volume of the ventral striatum in adults with ADHD that was not demonstrable using conventional MRI. The authors postulated that differences in striatal iron content may explain differential sensitivity of children and adults with ADHD to conventional MRI. Indeed, the same study found evidence for increased iron content in the striatum of adults with ADHD compared to children with ADHD.

Molecular imaging studies also suggest commonalities between PD and ADHD. Loss of nigrostriatal DA neurons in PD is associated with decreases in the dorsal striatum of multiple markers of DA function, including DA, DA metabolites, and membrane and vesicular DA transporters (DAT and VMAT, respectively).[77,78] The most studied marker of striatal DA function in ADHD is DAT. Both increases and decreases in striatal DAT have been reported in ADHD. A meta-analysis of these studies found that much of this variation across studies is accounted for by variation in the stimulant exposure history of subjects.[79] Striatal DAT levels tend to be lower in drug-naive ADHD patients than in those who received long-term stimulant therapy.

Deficits in mesolimbic DA are also demonstrable in both PD and ADHD. Mesolimbic DA neurons project from the VTA to the ventral striatum (nucleus accumbens and olfactory tubercle).[80] Structural pathology, including decreased volume, and decreased DA concentration are demonstrable in the nucleus accumbens of patients with PD.[81–84] Using conventional MRI technology, children with ADHD have decreased volume of the nucleus accumbens and other limbic structures.[75] As noted above, adults with ADHD have decreased volume of the ventral striatum when studied using MTI.[66]

The mesolimbic DA pathway to the nucleus accumbens plays a central role in mediating natural and drug-induced reward.[85,86] Deficits in reward processing occur in both PD and ADHD. Mesolimbic-associated clinical presentations in PD include apathy, anhedonia, and deficits in reward-based learning.[87,88] The latter appears to result from an impaired response to reward anticipation rather than processing related to reward receipt.[88–90] The most consistent and frequently reported manifestation of deficit reward processing in ADHD is an aversion to delay of gratification. Children and adults with ADHD tend to choose smaller immediate rewards over larger delayed rewards.[91–93] This characteristic in ADHD, like the impairment in PD, appears to result from diminished striatal DA signaling related to reward anticipation.[92,94–97]

NEUROPSYCHOLOGICAL FEATURES OF EARLY-STAGE PD AND ADULT ADHD, AND THEIR NEURAL CORRELATES

It has been suggested that ADHD symptoms may precede the motor symptoms of PD.[1] This raises the possibility that adult ADHD may be part of the PD prodrome. In this section the neuropsychological profile of early-stage PD (PD-ES) is compared

to that of adult ADHD. For the purpose of the following discussion, PD-ES is defined as either newly diagnosed PD, PD with disease duration of two or fewer years, or PD that has not advanced beyond Hoehn and Yahr stage 2.[98] Adult ADHD is defined as ADHD present in persons aged 18 or older. A comprehensive review of the neuropsychology of PD-ES and adult ADHD is beyond the scope of this article. Accordingly, the following discussion focuses on neuropsychological features that have been assessed in both conditions.

Comparative Neuropsychology of PD-ES and Adult ADHD

Comparison of the results of neuropsychological testing in PD-ES and adult ADHD is fraught with conceptual and methodological difficulty. To varying degrees, neuropsychological tests assess multiple cognitive, perceptual, affective, and behavioral domains. Which domains particular tests assess is a frequent topic of discussion and debate.[99–104] Different investigators may characterize the domains assessed by particular tests differently. For example, the cognitive domain assessed by the Trail Making Test Part B is variously characterized as attention[105,106] or as motor control and cognitive flexibility.[107–110] In addition, many neuropsychological tests have multiple subtests that are designed to tap different processes. Different studies using a given test may report or combine results of subtests differently, leading to apparent inconsistencies. Adding to the difficulty, there are often multiple ways to score particular tests, which do not necessarily have common psychometric properties or tap common domains and neural processes.[111–113] Finally, samples of persons with PD-ES and adult ADHD used in the studies discussed below are often clinically heterogenous, which, no doubt, accounts for much of the inconsistency across studies.[107,114–118] For all of these reasons, it is important to be as precise as possible about subject characteristics and the particular tests and measures used when comparing results across studies and clinical populations.

Notwithstanding these caveats, some tentative conclusions about the comparative neuropsychology of PD-ES and adult ADHD can be offered. Table 1 shows the neuropsychological tests that have been employed in both groups and whether individual studies report impairment or not. Studies that have employed standard neuropsychological tests of executive function[137]—including Stoop interference tests, trail making tests, backward digit span tests, semantic fluency tests, card sorting tests, and tower tests—report impairments in both PD-ES patients[105,106,119–122,132,133,135,136] and adults with ADHD.[107–110,123–127,129,131,134] In terms of cognitive domains, these studies suggest that both groups have impairments in core domains of executive function, including working memory, cognitive flexibility, inhibitory control, and planning.[102–104,113,138] Diverse memory impairments have also been reported in PD-ES patients[105,122,132,133,135] and adults with ADHD,[108,109,130,139] including deficits in immediate and delayed recall and recognition, which are classic measures of episodic memory.[140,141] Short-term memory—assessed by the digit span forward test—does not appear to be impaired in PD-ES.[105,106,122] The digit span forward test has produced mixed results in adults with ADHD.[107,109,110,128] A wide range of attentional deficits have been reported in adult ADHD, including impaired selective, divided, and sustained attention.[108,142–144] Although many of the neuropsychological tests that have been employed in PD-ES tap attentional processes, there is a paucity of research on attention per se in this group, though impairment on the Brief Test of Attention, a measure of auditory divided attention,[145] in PD-ES has been reported.[132] A large body of evidence exists regarding cognitive function in persons at risk for subsequent development of PD. These studies show, with considerable consistency (although see Marchand et al.[146] and Weintraub et al.[147]), that such persons have impairments in executive functions, attention, and memory.[35,148–154] The studies on the neuropsychological deficits that precede PD are particularly important because they are consistent with the idea that the cognitive deficits of adult ADHD may be part of the PD prodrome.

PD-ES, Adult ADHD, and Mild Cognitive Impairment

Another possible area of clinical overlap between PD-ES and adult ADHD is mild cognitive impairment (MCI). MCI—along with its corollary, mild neurocognitive disorder, from the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*—are diagnostic categories for cognitive decline, indicated by subjective complaints and neuropsychological test evidence, that does not substantially impair adaptive functioning.[4,115] The concept of MCI evolved from efforts to define and diagnose a transition stage between normal cognition and dementia in Alzheimer's disease.[155–157] Diagnosis of MCI is also associated with increased risk for developing dementia in Parkinson's disease.[118,158] Approximately 20% to 40% of PD-ES patients meet Movement Disorder Society criteria for MCI.[133,159–162] Depending on the extent of neuropsychological testing performed, those criteria for Parkinson's disease with MCI (PD-MCI) allow for classification into four PD-MCI subtypes.[115] Amnestic and non-amnestic subtypes are based on presence or absence of memory impairment. These two categories can be further divided based on whether the impairment is in a single domain or multiple domains. Among drug-naive PD-ES patients, the amnestic multidomain MCI subtype is the most common.[159] Impairments in executive function, memory, attention, and visuospatial function have been reported in PD-ES with MCI.[133,159] A recent study found that multi-domain MCI may be a part of the PD prodrome.[148]

The relationship between MCI and adult ADHD is unclear. The cognitive features of MCI overlap substantially with the cognitive impairments in adult ADHD.[163] This overlap can make it difficult to distinguish between these syndromes.[164] Nevertheless, a recent study found that adults with ADHD were no more likely to score in the MCI range on the Montreal Cognitive Assessment than persons without ADHD.[165]

Table 1

Studies Reporting Results of Neuropsychological Tests in Persons with Early-Stage Parkinson's Disease or Adult ADHD

Test	Early-stage Parkinson's disease		Adult ADHD	
	Impaired	Not impaired	Impaired	Not impaired
Stroop interference test	Henik et al. (1993)[119] Dujardin et al. (1999)[120] Aarsland et al. (2009)[121] Broeders et al. (2013)[122]	Muslimović et al. (2005)[106]	King et al. (2007)[123] Antshel et al. (2010)[124] Boonstra et al. (2010)[125] Fuermaier et al. (2013)[109] Fuermaier et al. (2015)[108] Kakuszi et al. (2016)[126]	Johnson et al. (2001)[127] Saboya et al. (2009)[128] Pazvantoğlu et al. (2012)[129] Butzbach et al. (2019)[130]
Trail Making Test Part A	Muslimović et al. (2005)[106] Elgh et al. (2009)[105] Broeders et al. (2013)[122]		Murphy (2002)[131] Mostert et al. (2015)[107]	Johnson et al. (2001)[127] Saboya et al. (2009)[128] Rohlf et al. (2012)[110] Pazvantoğlu et al. (2012)[129]
Trail Making Test Part B	Muslimović et al. (2005)[106] Elgh et al. (2009)[105] Broeders et al. (2013)[122]		Johnson et al. (2001)[127] Murphy (2002)[131] Rohlf et al. (2012)[110] Pazvantoğlu et al. (2012)[129] Fuermaieret al. (2013)[109] Mostert et al. (2015)[107] Fuermaieret al. (2015)[108]	Saboya et al. (2009)[128] Butzbach et al. (2019)[130]
Digit Span Forward		Muslimović et al. (2005)[106] Elgh et al. (2009)[105] Broeders et al. (2013)[122]	Fuermaier (2013)[109] Mostert et al. (2015)[107]	Saboya et al. (2009)[128] Rohlf et al. (2012)[110]
Digit Span Backward	Muslimović et al. (2005)[106] Broeders et al. (2013)[122] Kalbe et al. (2016)[132]	Elgh et al. (2009)[105]	Boonstra et al. (2010)[125] Rohlf et al. (2012)[110] Mostert et al. (2015)[107]	Saboya et al. (2009)[128] Fuermaier et al. (2013)[109] Butzbach et al. (2019)[130]
Category (semantic) fluency	Muslimović et al. (2005)[106] Elgh et al. (2009)[105] Aarsland et al. (2009)[121] Broeders et al. (2013)[122] Pereira et al. (2014)[133] Kalbe et al. (2016)[132]		Tucha et al. (2005)[134] Mostert et al. (2015)[107]	Boonstra et al. (2010)[125]
Letter (phenomic) fluency	Broeders et al. (2013)[122] Pereira et al. (2014)[133]	Elgh et al. (2009)[105]	Tucha et al. (2005)[134] Fueramier et al. (2013)[109] Mostert et al. (2015)[107]	Johnson et al. (2001)[127] Boonstra et al. (2010)[125] Fuermaier et al. (2015)[108]
Card sorting tests	Levin et al (1988)[135] Elgh et al. (2009)[105] Broeders et al. (2013)[122] Kalbe et al. (2016)[132]		Antshel et al. (2010)[124] Rohlf et al. (2012)[110]	Johnson et al. (2001)[127] Saboya et al. (2009)[128] Boonstra et al (2010)[125]
Tower tests	Foltynie et al. (2004)[136] Broeders et al. (2013)[122]		Murphy (2002)[131]	Saboya et al. (2009)[128] Boonstra et al. (2010)[125]

ADHD, attention-deficit/hyperactivity disorder.

A related issue is whether ADHD is associated with dementia. Indeed, there has been speculation that adult ADHD and dementia may be different points along a pathophysiological continuum.[163,166] The results of research on this topic are mixed. Ivanchak and colleagues[167] did not find an association between retrospectively diagnosed ADHD and dementia in geriatric subjects. By contrast, a recent large-scale, population-based cohort study in Taiwan found that the risk for developing dementia is increased 3.4-fold in adults with ADHD compared to matched non-ADHD controls.[168] A case-control study found that Lewy body dementia and Alzheimer's disease are associated with adult symptoms of ADHD.[169] Another cohort study in the United States found that a severe ADHD phenotype is associated with increased hospitalization for Lewy body dementia and Alzheimer's disease.[170] All of these studies have methodological limitations. Nevertheless, the weight of the extant evidence, albeit sparse, suggests an association between adult ADHD and subsequent development of dementia.

Neural Correlates of Cognitive Impairments in PD-ES and Adult ADHD

Numerous studies have been conducted to elucidate the neural mechanisms that underlie cognitive impairment in PD-ES and PD-MCI patients. Cortical thinning or morphometric changes in PD-ES or PD-MCI patients have been reported in prefrontal, temporal, parietal, occipital, and insular cortices, and in numerous subcortical structures, including the caudate, amygdala, nucleus accumbens, thalamus, putamen, and hippocampus.[171–176] Some of these structural changes have been correlated with deficits in cognitive function. The hippocampus and associated structures have been specifically implicated in memory impairment in PD-ES and PD-MCI. Compared to PD patients with normal cognition (PD-NC), PD-MCI patients have decreased hippocampal volume, which in non-demented PD patients is correlated with memory impairment on the memory subscale of the Dementia Rating Scale.[176] Compared to healthy controls, drug-naive PD-ES patients have hippocampal atrophy, which is correlated with performance on the Wechsler Memory Scale–Revised.[172] In addition, compared to PD-NC patients, drug-naive PD-ES patients with MCI display atrophy of the entorhinal cortex;[174] which serves as the major relay between cortico-hippocampal circuits involved in memory;[177,178] in PD-MCI patients, decreased volume of the entorhinal cortex is correlated with memory impairment, assessed by the Hopkins Verbal Learning Test.[174] Impaired sustained attention has been associated with atrophy of the prefrontal cortex in PD-ES patients.[172]

Functional imaging studies have also found neural correlates of cognitive impairments in PD-ES and PD-MCI. Drug-naive PD-ES patients with MCI compared to PD-NC patients had increased activity in the right inferior frontal and left fusiform gyri, and activity in the right inferior frontal gyrus was negatively correlated with the Montreal Cognitive Assessment score, category fluency, and the Symbol Digit Modalities Test,[179] the last being a measure of speed and efficiency of neural processing.[180] PD-MCI, compared to PD-NC, patients have prolonged arterial transfer time in the right thalamus, which is negatively correlated with semantic fluency,[181] a commonly used measure of executive function.[104]

Structural and functional imaging studies have implicated the cerebellum in neuropsychological deficits in PD, including PD-ES. Although historically controversial, a role for the cerebellum in cognition and affect is now generally accepted.[182,183] Atrophy of the cerebellum is associated with cognitive and affective impairments in PD.[184–187] In PD-ES, altered connectivity between the cerebellum and a variety of cortical and subcortical regions has been reported.[188,189]

Numerous functional imaging studies have been conducted to evaluate neural correlates of neuropsychological impairment in adult ADHD. Functional imaging has been conducted during tasks designed to assess working memory,[190–194] more complex mixtures of executive functions (e.g., set shifting/inhibition/executive attention/working memory),[195–199] various aspects of reward processing,[200–205] and attention/inhibition.[200,204,206] Studies employing working-memory tasks have found activation differences between persons with adult ADHD and non-ADHD controls in multiple forebrain, midbrain, and hindbrain regions. The brain regions that have been most frequently reported to exhibit altered activity during working-memory tasks in adults with ADHD are various regions of the cerebellum and prefrontal cortex.[190,192–194] The most frequently reported brain region to exhibit altered activity in adults with ADHD during tasks that tap multiple executive functions is the cingulate cortex.[195–199] Other areas that exhibited altered activity in adults with ADHD during tasks that tap multiple executive functions include areas of the prefrontal cortex, such as the dorsolateral prefrontal cortex and orbitofrontal cortex,[195,197] dorsal striatum,[197,199] and insula.[195,197] During tasks involving reward processing, adults with ADHD have been reported to have altered activity in prefrontal cortical areas, including the ventromedial prefrontal and orbitofrontal cortices,[200,201,204,205] dorsal and ventral striatum,[201,202,204,205] and anterior cingulate.[201,203,204] Functional imaging during tests of attention/inhibition revealed altered activity in prefrontal and parietal areas, dorsal striatum, thalamus, anterior cingulate, and cerebellum.[200,204,206] Perhaps the safest generalization that can be drawn from these disparate findings is that cognitive impairments in adults with ADHD are associated with altered activity in fronto-striato-cerebellar networks, which is consistent with the conclusions of others.[190,200,207,208]

Cognitive deficits in PD-ES and PD-MCI are associated with DA dysfunction in cortico-striatal circuits that are implicated in executive function. Christopher and colleagues,[209] using PET imaging, reported that PD-MCI patients, compared to PD-NC patients and healthy controls, had significantly decreased indices of DA function in the associative striatum and reduced D2 receptors in the insula, the latter effect being correlated with a composite measure of executive

function. PD-MCI patients in this study were not early stage. Decreased striatal DA function was present in PD-MCI patients, however, after controlling for disease severity. Schragg and colleagues[210] found that results of SPECT imaging for caudate DAT contributed to prediction of cognitive decline (Montreal Cognitive Assessment score) in drug-abstinent PD-ES patients. Siepel and colleagues,[211] also using SPECT imaging, found that DAT binding in the caudate and putamen in drug-naive PD-ES patients is associated with impairment in executive function and attention. Another PET study revealed area-specific increases and decreases in floro-L-dopa uptake in the frontal cortex and striatum, respectively, in drug-naive PD-ES patients compared to healthy controls; performance on a test of vigilance was positively correlated with uptake in the dorsolateral prefrontal cortex, and performance on the Stroop test was negatively correlated with uptake in the medial frontal and anterior cingulate cortices.[212] Williams-Gray and colleagues[213] reported that a particular variant of the COMT gene, which codes for an enzyme involved in DA metabolism, is correlated with executive function assessed by the Tower of London Test in PD-ES patients. Finally, decreased striatal DA function has also been linked to cognitive impairment in prodromal PD.[147,149]

A relative paucity of studies have examined the association of DA function with cognitive impairment in adults with ADHD. There is evidence for correlations between DA receptor and DAT binding in the dorsal and ventral striatum on measures of interference/inhibition, inattention, and motivation in this group.[93,214–218]

Comorbid Psychiatric Disorders in PD-ES and Adult ADHD

Comorbid psychiatric disorders are another area of overlap between PD-ES and adult ADHD. PD-ES and PD-MCI patients have increased occurrence of depressive and anxiety disorders.[219–221] In PD-MCI, symptoms of depression and anxiety are more strongly associated with the amnestic than non-amnestic MCI subtype.[222] Depression in PD-MCI is positively correlated with apathy,[220] though depression and apathy are separable disorders.[223] A large body of evidence indicates that depressive and anxiety disorders are part of the PD prodrome.[224–228] Indeed, depression, in particular, is among the diagnostic criteria for prodromal PD.[229] Although research is mixed on how early it is that depressive and anxiety disorders emerge before the motor symptoms of PD, some studies have indicated that it may be as much as 15 to 20 years,[224,226] indicating that these disorders are not necessarily secondary to the disabling symptoms of PD. Moreover, patients with PD have higher rates of depression than those with other chronic disabling diseases.[230] Depression in advanced PD has been linked to pathological changes in raphe nuclei,[231] the site of ascending serotonin neurons. A paucity of research is available on the pathophysiology of depression and anxiety in PD-ES and prodromal PD.

Adults with ADHD have increased risk for depression.[232–235] The mechanisms that mediate this association are unknown. Based largely on results of family and twin studies, Faraone and Larsson[236] proposed that ADHD and depression are associated because they share common genetic etiologies. An alternative hypothesis that has received considerable attention posits that depression is caused by the adverse consequences of ADHD, such as impaired peer and family relationships and low academic achievement. Research designed to test this hypothesis indicates that such variables account for a substantial amount of the variance in depression in adolescents with ADHD.[237–239] Systematic investigation into the variables that mediate the association between adult ADHD and depression is lacking. Nevertheless, on the assumption that ADHD is a developmental disorder, an important feature of the association between adult ADHD and depression is that the former precedes the latter. This is borne out by empirical research.[240] As noted above, the opposite temporal relationship exists between the onset of PD and depression. This could suggest that the mechanisms that underlie the association with depression are different in these disorders or that ADHD and depression are part of the PD prodrome.

STIMULANTS AND PARKINSON'S DISEASE

Two clinical conditions can be associated because the treatment for one directly causes the other. Amphetamines and methylphenidate are the principal medications used to treat ADHD. It has been suggested that the association between PD and ADHD may be explained, in part, by toxic effects of these drugs on DA neurons.[241] Amphetamine, methamphetamine, and methylphenidate are distinct chemicals, and, where it is important, they are discussed separately below. However, due to the considerable overlap of pharmacological profiles of amphetamine and methamphetamine, in certain contexts it is convenient to discuss these drugs together.

Much of the research on stimulant neurotoxicity has focused on methamphetamine because of its widespread abuse. The research on animals and human methamphetamine abusers is clear—methamphetamine and other amphetamines are toxic to mesencephalic DA neurons. Indeed, methamphetamine-induced neurotoxicity is used to model PD in animals.[242] In mice, rats, and monkeys, prolonged exposure to methamphetamine/amphetamine (meth/amph) causes cell loss in the SN,[243–245] degeneration of striatal DA axon terminals,[243,246–248] decreases in striatal DA and DAT, and decreased DAT function.[249–256] The pattern of neurotoxic changes induced by methamphetamine parallels the DA deficits seen in PD. In monkeys, the methamphetamine-induced decrease in DA concentration is greatest in the putamen, followed by the caudate and then the nucleus accumbens, and toxic change in SN DA neurons is greater than in VTA neurons.[250] It has been reported that, in monkeys, methamphetamine-induced decreases in striatal DA markers occur without decreases in cell numbers in the ventral midbrain, suggesting that the terminals of DA neurons are more affected than cell bodies.[244] In the same study, substantial recovery of striatal DAT occurred after 1.5 years. However, another

study, also in monkeys, found that neurotoxic effects of methamphetamine lasted for up to four years after exposure.[257]

Numerous diverse findings point to pathologic changes in DA systems in human chronic meth/amph abusers. Echogenicity of the substantia nigra is increased in abstinent adult meth/amph abusers,[258–260] and the degree of this increase is positively correlated with the duration of meth/amph abuse and the estimated amount of lifetime methamphetamine intake.[258] Persons with a history of meth/amph abuse have increased Parkinson motor symptoms.[258,260] Postmortem studies of striatal tissue of meth/amph abusers show significant reductions in several indices of DA function, including DA, DAT, VMAT, and tyrosine hydroxylase, in numerous DA terminal regions, including the caudate, putamen, and nucleus accumbens.[261–263] PET studies show reduced DAT density in abstinent meth/amph abusers.[264–266] DAT levels begin to recover after a year of abstinence[267] but remain decreased for up to three years.[265] Finally, several epidemiological and case-control studies have shown an association between history of meth/amph abuse and increased risk for subsequent or early development of PD or increased parkinsonism.[260,268–273]

An important question is whether amphetamines, as they are used clinically to treat ADHD, are toxic to DA neurons. In most of the animal and human studies cited above, stimulant exposure levels are high relative to clinical doses, and dosing regimens (as stimulants) rarely mimic the manner in which these drugs are used clinically. The study by Ricaurte and colleagues[248] is an exception. In that study, baboons orally self-administered a racemic (3:1 d/l) amphetamine mixture twice daily in increasing doses ranging from 2.5 to 20 mg/day for four weeks. Plasma amphetamine concentrations, measured at one-week intervals, were comparable to those observed in children taking amphetamine for ADHD. Two to four weeks after cessation of amphetamine treatment, multiple markers of striatal DA function were decreased, including DA and DAT. In another group of animals (squirrel monkeys), d/l amphetamine blood concentration was titrated to clinically comparable levels for four weeks by administering varying doses of amphetamine by orogastric gavage. These animals also had decreased markers of striatal DA function assessed two weeks after cessation of amphetamine.

Methylphenidate (MPH) appears to be substantially less neurotoxic than meth/amph. MPH had no effect on survival of embryonic DA cells in vitro but rather had a protective effect against the DA neurotoxin 1-methyl-4-phenylpyridinium.[274] Repeated administration of MPH to adult rats (50 mg/kg for 30 days,[254] 100 mg/kg for 4 days[275]) or to adult rhesus monkeys (1–96 mg/kg for 6 months)[254] had no effect on striatal DA. By contrast, repeated doses (10–40 mg/kg, every 2 hours × 4) of MPH in adult mice caused a short-term decrease in striatal DA.[255] These doses and higher doses (80–100 mg/kg every 2 hours × 4) had no long-term effect on striatal DA.[255] Some evidence suggests that MPH may be more toxic during early brain development. Prolonged exposure (once daily for 5 days/week for 12 weeks) of young mice to a relatively low dose (10 mg/kg) of MPH produced gliosis and a ~20% decline in DA neurons in the substantia nigra.[276] Similarly, administration of MPH (2 mg/kg/day for 2 weeks) in prepubertal, but not post-pubertal, rats produced a prolonged decrease in striatal DAT.[277] By contrast, two studies designed to mimic prolonged developmental exposure in children using dosing regimens that produced MPH blood levels in the clinical therapeutic range (15–25 ng/ml) in rhesus monkeys found no effect of MPH treatment on DAT or DA receptors.[278,279]

The mechanisms responsible for differential meth/amph and MPH neurotoxicity are unclear. Oxidative stress, excitotoxicity, and mitochondrial dysfunction have all been implicated in the neurotoxic actions of both meth/amph and MPH.[280–282] Recent evidence suggests that stimulant neurotoxicity is mediated by effects on protein folding. As noted above, misfolding of α-synuclein is associated with neurodegeneration in PD. Amphetamine binds preferentially to the N-terminus of α-synuclein and enhances misfolding, whereas MPH binds to both the N- and C-termini, resulting in a loop structure that inhibits misfolding.[283]

The unambiguous neurotoxicity of meth/amph is worrisome. Use of prescription meth/amph formulations in the United States doubled between 2006 and 2016, and exceeded that of MPH in 2016.[284,285] By contrast, in other developed regions of the world, MPH is still the most widely used stimulant.[286,287] The National Survey on Drug Use and Health 2015–2016 found that 16 million adults in the United States used prescription stimulants.[288] The prevalence of 30-day prior use of prescription meth/amph among U.S. children and adolescents was 1.3% between 2011 and 2014. Among children aged 6 to 11, the prevalence of meth/amph use in this period was 2.1%.[284] If meth/amph, as it is used clinically, is toxic to DA neurons, the rising clinical use of amphetamines in the United States may portend increases in PD in the coming years.

POSSIBLE LINKAGE MECHANISMS

If PD and ADHD are associated clinical entities, then understanding the mechanisms responsible for this association could provide insights into the etiology and pathogenesis of both disorders. One possible explanation for an association between PD and ADHD is that both are causally related to a common exposure. The study that provides the principle epidemiological evidence for a link between PD and ADHD[2] controlled for some potential confounding exposures (e.g., antipsychotic and tobacco use) but not for others. Potentially relevant variables that were not controlled include traumatic brain injury and exposure to environmental toxins. Antecedent traumatic brain injury increases risk for both PD and ADHD,[289,290] and both disorders are associated with lead, mercury, and pesticide exposure.[291–296] Additional epidemiological studies are needed to assess the contribution of such variables to the association between PD and ADHD.

Genetic factors may also mediate an association between PD and ADHD. ADHD has a strong familial component (h^2 = ~0.75).[236] As noted above, although environmental

factors play a major role in sporadic PD, genetic factors are important.[15] A possible genetic linkage between PD and ADHD has been investigated. Analysis of nine ADHD candidate genes, chosen for their involvement in the regulation of monoamine neurotransmitters, showed no association with PD.[297] By contrast, ADHD is associated with copy-number variations in *PARK2*.[298] Mutations in *PARK2* occur in ~10% to ~20% of cases with early-onset, sporadic PD.[12,299] If PD and ADHD are associated by virtue of an association with *PARK2*, it might be expected that ADHD would be more strongly associated with early- than late-onset PD. The study by Curtin and colleagues[2] did not find an association between ADHD and age at onset of BG&C.

There is intriguing evidence that ADHD, like PD, may be associated with Lewy pathology. Golimstok and colleagues[169] reported that ten-year antecedent ADHD symptoms are significantly increased in patients with Lewy body dementia compared to both controls and patients with Alzheimer's disease. Fluegge and Fluegge[170] reported that antecedent severe ADHD was associated with an increase in hospitalization for both Lewy body dementia and Alzheimer's disease. Between ~30% and ~50% of patients with AD also have Lewy pathology.[300] Thus, ADHD has been associated with three neurodegenerative disorders, all of which are also associated with Lewy pathology. Another intriguing finding is that α-synuclein expression is increased in experimental models of traumatic brain injury[301–303] and by environmental neurotoxins that are associated with both PD and ADHD.[291,303] Although, as noted above, the nature of the relationship between Lewy pathology and neurodegeneration is unclear, these findings raise the possibility that α-synuclein may be a biomarker for both ADHD and PD. Clinical-pathological studies necessary to evaluate this hypothesis do not appear to have been undertaken.

Another possible explanation for an association between PD and ADHD is that stimulant medication damages DA neurons and either causes parkinsonism or exacerbates the damage to DA neurons caused by other factors. The study by Curtin and colleagues[2] found that medical use of stimulant medication in ADHD is associated with a 6- to 8-fold increase in the risk for BG&C. One possible explanation for this finding—in fact, the one preferred by the authors—is that stimulant treatment is a marker for severe ADHD and that severe ADHD is an independent risk factor for BG&C. In support of this hypothesis, Curtin and colleagues[2] reported that the risks for both BG&C and PD are significantly increased 1.8- and 2.3-fold, respectively, in ADHD patients with no known history of prescription stimulant use or stimulant abuse. By contrast, it is possible that ADHD patients in this study had stimulant exposure that was not recorded in the medical records. A particularly puzzling finding by Curtin and colleagues[2] is that the risk for BG&C is increased 8-fold among persons with ADHD who had a known history of medical use of MPH alone. This finding is difficult to reconcile with the substantial evidence (discussed above) that MPH is less toxic than meth/amph. Another curiosity in the Curtin and colleagues[2] data is that the stimulant effect was significant for the composite outcome BG&C—which included PD, secondary PD, other diseases of the basal ganglia, and essential tremor—but not for PD alone. Although the composite outcome was used to increase diagnostic sensitivity, it may have also decreased specificity.[304] Thus, disorders distinct from PD may have contributed to the stimulant effect. The nature of the relationship between stimulant exposure in ADHD and risk for subsequent development of PD obviously needs further investigation.

CONCLUSION

Epidemiological evidence indicates that persons with a diagnosis of ADHD have increased risk for the subsequent development of Parkinson's disease. The central question raised by this observation is: what is the nature of this relationship? The structural, functional, and molecular neuroimaging studies reviewed here indicate that PD and ADHD share a common neurobiological substrate involving perturbations of mesostriatal DA neurons. Another relevant finding is that adults with ADHD and persons with prodromal PD or PD-ES have similar neuropsychological profiles. The comparative neuropsychology of these conditions reveals common deficits in executive function, memory, attention, and inhibition. Neuroimaging studies reveal complex differences in the brain structures and networks that mediate these deficits in PD-ES and adult ADHD. However, frontostriatal circuits are implicated in both. Collectively, these disparate lines of evidence are consistent with the possibility that ADHD, prodromal PD, PD-ES, and PD are sequential manifestations of a common pathophysiological continuum.

Nevertheless, much additional research is needed to assess this hypothesis. As noted previously, subject heterogeneity and methodological differences make it difficult to compare neuropsychological studies of adults with ADHD and persons who have prodromal features or are in the early stages of PD. Additional neuropsychological studies that employ a uniform set of measures and methodologies in more homogenous subject samples are needed, and future studies of adults with ADHD should be expanded beyond neuropsychological testing to include other markers for prodromal PD (e.g., REM sleep behavior disorder, anosmia, constipation) and also PD biomarkers (e.g., Lewy pathology). A related issue that has not been taken into consideration is whether adult ADHD is a unitary construct or one that subsumes distinct clinical entities. Notwithstanding the widely held view that ADHD is a developmental disorder, current evidence indicates that ADHD can occur in adults de novo.[305] It is conceivable that developmental- and adult-onset forms of ADHD may be differentially associated with PD.

The mechanisms responsible for the association between PD and ADHD are not known. The evidence reviewed here does not support a strong genetic linkage. Thus, environmental exposures seem likely to mediate the association. Among the possible environmental exposures, stimulant treatment of ADHD is the most salient. Further research on the possible

link between clinical use of stimulants and PD is urgently needed. Avenues for future research are suggested above. If an association between clinical use of stimulants and PD or related disorders is confirmed, it could have serious implications for therapeutics and public health.

Declaration of interest: The author reports no conflicts of interest. The author alone is responsible for the content and writing of the article.

REFERENCES

1. Walitza S, Melfsen S, Herhaus GH, et al. Association of Parkinson's disease with symptoms of attention deficit hyperactivity disorder. J Neural Transm (Vienna) 2007;suppl 72:311–5.
2. Curtin K, Fleckenstein AE, Keeshin BR, et al. Increased risk of diseases of the basal ganglia and cerebellum in patients with a history of attention-deficit/hyperactivity disorder. Neuropsychopharmacology 2018;43:2548–55.
3. Tindle HA, Duncan MS, Greevy RA, et al. Lifetime smoking history and risk of lung cancer: results from the Framingham Heart Study. J Natl Cancer Inst 2018;110:1201–7.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing, 2013.
5. Campenhausen von S, Bornschein B, Wick R, et al. Prevalence and incidence of Parkinson's disease in Europe. Eur Neuropsychopharmacol 2005;15:473–90.
6. Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson's disease in advanced age. Neurology 2009;72:432–8.
7. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. Lancet Neurol 2006;5:525–35.
8. Muangpaisan W, Hori H, Brayne C. Systematic review of the prevalence and incidence of Parkinson's disease in Asia. J Epidemiol 2009;19:281–93.
9. Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17:939–53.
10. Pringsheim T, Jette N, Frolkis A, Steves TDL. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2014;29:1583–90.
11. Rajput AH, Birdi S. Epidemiology of Parkinson's disease. Parkinsonism Relat Disord 1997;3:175–86.
12. Crosiers D, Theuns J, Cras P, Van Broeckhoven C. Parkinson disease: insights in clinical, genetic, and pathological features of monogenic disease subtypes. J Chem Neuroanat 2011; 42:131–41.
13. Tanner CM, Ottman R, Goldman SM, et al. Parkinson's disease in twins. An etiologic study. JAMA 1999;281:341–6.
14. Marder K, Levy G, Louis ED, et al. Familial aggregation of early- and late-onset Parkinson's disease. Ann Neurol 2003; 54:507–13.
15. Zhang P, Chen Y, Zhang C, Wang Y, Fernandez-Funez P. Genetics of Parkinson's disease and related disorders. J Med Genet 2018;55:73–80.
16. Chai C, Lim K. Genetic insights into sporadic Parkinson's disease pathogenesis. Curr Genomics 2013;14:486–501.
17. Papapetropoulos S, Adi N, Ellul J, Argyriou AA, Chroni E. A prospective study of familial versus sporadic Parkinson's disease. Neurodegener Dis 2007;4:424–7.
18. Lubbe S, Morris HR. Recent advances in Parkinson's disease genetics. J Neurol 2014;261:259–66.
19. Langston JW, Ballard PA, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. Science 1983;219:979–80.
20. Langston JW, Forno LS, Rebert CS, Irwin I. Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyrine (MPTP) in the squirrel monkey. Brain Res 1984;292:390–4.
21. Kalia LV, Lang AE. Parkinson's disease. Lancet 2015;386: 896–912.
22. Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson's disease. Ann Neurol 2012;72:893–901.
23. Adler CH, Beach TG, Hentz JG, et al. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. Neurology 2014;83:406–12.
24. Marsili L, Rizzo G, Colosimo C. Diagnostic criteria for Parkinson's disease: from James Parkinson to the concept of prodromal disease. Front Neurol 2018;9:156.
25. Erro R, Picillo M, Vitale C, et al. (2013). Non-motor symptoms in early Parkinson's disease: a 2-year follow-up study on previously untreated patients. J Neurol Neurosurg Psychiatry 2013;84:14–7.
26. Goldman JG, Postuma R. Premotor and non-motor features of Parkinson's disease. Curr Opin Neurol 2014;27:43441.
27. Mahlknecht P, Seppi K, Poewe W. The concept of prodromal Parkinson's disease. J Parkinsons Dis 2015;5:681–97.
28. Postuma RB, Lang AE, Gagnon JF, Pelletier A, Montplaisir JY. How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behavior disorder. Brain 2012;135:1860–70.
29. Claassen DO, Josephs KA, Ahlkog JE, Silber MH, Tilmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. Neurology 2010;75:494–9.
30. Postuma RB, Gagnon JF, Bertrand JA, Marchand DG, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder. Neurology 2015;84:1104–13.
31. Lin CH, Lin JW, Liu YC, Chang CH. Risk of Parkinson's disease following severe constipation: a nationwide population-based cohort study. Parkinsonism Relat Disord 2014;20:1371–5.
32. Savica R, Carlin JM, Grossardt B. Medical records documentation of constipation preceding Parkinson's disease. Neurology 2009;73:1752–8.
33. Yu Q, Yu S, Zuo L, et al. Parkinson disease with constipation: clinical features and relevant factors. Sci Rep 2018;8:567.
34. Ross GW, Petrovitch H, Abbott RD, et al. Association of olfactory dysfunction with risk for future Parkinson's disease. Ann Neurol 2008;63:167–73.
35. Darweesh SKL, Wolters FJ, Postuma RB, et al. Association between poor cognitive functioning and risk of incident Parkinsonism: the Rotterdam Study. JAMA Neurol 2017;74:1431–8.
36. Schrag A, Anastasiou Z, Ambler G, Noyce A, Walters K. Predicting diagnosis of Parkinson's disease: a risk algorithm based on primary care presentations. Mov Disord 2019;34:480–6.
37. Beyer K, Domingo-Sàbat M, Ariza A. Molecular pathology of Lewy body diseases. Int J Mol Sci 2009:10:724–45.
38. Goedert M, Spillantini MG, Tredici KD, Braak H. 100 years of Lewy pathology. Nat Rev Neurol 2013;9:13–24.
39. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the α-synuclein gene identified in families with Parkinson's disease. Science 1997;276:2045–7.
40. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Goedert RJ. Alpha-synuclein in Lewy bodies. Nature 1997; 388:839–40.
41. Braak H, Rüb U, Gai WP, Tredici KD. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types

may be subject to neuroinvasion by an unknown pathogen. J Neural Transm (Vienna) 2003;110:517–36.
42. Braak H, Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. (2003b). Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197–211.
43. Braak H, Ghebremedhin E, Rüb U, Bratzke H, Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 2004;318:121–34.
44. Braak H, Tredici KD. Neuropathological staging of brain pathology in sporadic Parkinson's disease: separating the wheat from the chaff. J Parkinsons Dis 2017;7:S71–85.
45. Hawkes CH, Tredici K, Braak H. Parkinson's disease: a dual-hit hypothesis. Neuropathol Appl Neurobiol 2007;33:599–614.
46. Beach TG, White CL, Hladik CL, et al. Olfactory bulb α-synucleinopathy has high specificity and sensitivity for Lewy body disorders. Acta Neuropathol 2009;117:169–74.
47. Hawkes CH, Tredici K, Braak H. Parkinson's disease: the dual hit theory revisited. Ann N Y Acad Sci 2009;1170:615–22.
48. Saito Y, Shioya A, Sano T, Sumikura H, Murata M, Murayama S. Lewy body pathology involves the olfactory cells in Parkinson's disease and related disorders. Mov Disord 2016;31:135–8.
49. Shannon KM, Keshavazian A, Dodiya HB, Jakate S, Kordower JH. Is alpha-synuclein in the colon a biomarker for premotor Parkinson's disease? Evidence from 3 cases. Mov Disord 2012;27:716–9.
50. Chartier S, Duyckaerts C. Is Lewy pathology in the human nervous system chiefly an indicator of neuronal protection or of toxicity? Cell Tissue Res 2018;373:149–60.
51. Foffani G, Obeso JA. A cortical pathogenic theory of Parkinson's disease. Neuron 2018;99:1116–28.
52. Rietdijk CD, Perez-Pardo P, Garssen J, van Wezel RJA, Kraneveld AD. Exploring Braak's hypothesis of Parkinson's disease. Front Neurol 2017;8:37.
53. Dickson DW. Parkinson's disease and parkinsonism: neuropathology. Cold Spring Harb Perspect Med 2012;2:a009258.
54. Brichta L, Greengard P. Molecular determinants of selective dopaminergic vulnerability in Parkinson's disease: an update. Front Neuroanat 2014;8:152.
55. Damier P, Hirsch EC, Agid Y, Graybiel AM. The substantia nigra in human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain 1999;122(pt.8):1437–48.
56. Subraminiam M, Althof D, Gispert S, et al. Mutant α-synuclein enhances firing frequencies in dopamine substantia nigra neurons by oxidative impairment of A-type potassium channels. J Neurosci 2014;34:13586–99.
57. Barber TR, Klein JC, Mackay CE, Hu MTM. Neuroimaging in pre-motor Parkinson's disease. Neuroimage Clin 2017;15:215–27.
58. Berg D, Seppi K, Behnke S, et al. Enlarged substantia nigra hyperechogenicity and risk for Parkinson disease. Arch Neurol 2011;68:932–7.
59. Li D, He Y, Liu J, Chen S. Diagnostic accuracy of transcranial sonography of the substantia nigra in Parkinson's disease: a systematic review and meta-analysis. Sci Rep 2016;6:20863.
60. Toomsoo T, Lieplt-Scarfone I, Kerner R, Kadastik-Eerme L, Asser T. Substantia nigra hyperechogenicity. Validation of transcranial sonography for Parkinson disease diagnosis in a large Estonian cohort. J Ultrasound Med 2016;35:17–23.
61. Krauel K, Feldhaus HC, Simon A, et al. Increased echogenicity of the substantia nigra in children and adolescents with attention-deficit/hyperactivity disorder. Biol Psychiatry 2010; 68:352–8.
62. Romanos M, Weise D, Schiesser M, et al. Structural abnormality of the substantia nigra in children with attention-deficit hyperactivity disorder. J Psychiatry Neurosci 2010;35:55–8.
63. Berg D, Jabs B, Merschdorf U, Beckmann H, Becker G. Echogenicity of substantia nigra determined by transcranial ultrasound correlates with severity of parkinsonian symptoms induced by neuroleptic therapy. Biol Psychiatry 2001;50:463–7.
64. Wade R, Corbett M, Eastwood A. Quality assessment of comparative diagnostic accuracy studies: our experience using a modified version of the QUADAS-2 tool. Res Synth Methods 2013;4:280–6.
65. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
66. Sethi A, Evelyn-Rahr E, Dowell N, et al. Magnetization transfer imaging identifies basal ganglia abnormalities in adult ADHD that are invisible to conventional T1 weighted voxel-based morphometry. Neuroimage Clin 2017;15:8–14.
67. Lang AE, Lozano AM. Parkinson's disease. Second of two parts. N Engl J Med 1998;339:1130–43.
68. Tsui A, Isacson O. Functions of the nigrostriatal dopaminergic synapse and the use of neurotransplantation in Parkinson's disease. J Neurol 2011;258:1393–405.
69. Weingarten CP, Sundman MH, Hickey P, Chen N. Neuroimaging of Parkinson's disease: expanding views. Neurosci Biobehav Rev 2015;59:16–52.
70. Sterling NW, Lewis MM, Du G, Huang X. Structural imaging and Parkinson's disease: moving toward quantitative markers of disease progression. J Parkinsons Dis 2016;6:557–67.
71. Ellison-Wright I, Ellison-Wright Z, Bullmore E. Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. BMC Psychiatry 2008;8:51.
72. Frodl T, Skokauskas N. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatr Scand 2012;125:114–26.
73. Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. Am J Psychiatry 2011;168:1154–63.
74. Rubia K, Alegria AA, Brinson H. Brain abnormalities in attention-deficit hyperactivity disorder: a review. Rev Neurol 2014;58(suppl 1):S3–18.
75. Hoogman M, Bralten J, Hibar DP, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. Lancet Psychiatry 2017;4:310–9.
76. Proal E, Reiss PT, Klein RG, et al. Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. Arch Gen Psychiatry 2011;68:1122–34.
77. Kish SJ, Boileau I, Callaghan RC, Tong J. Brain dopamine neurone 'damage': methamphetamine users vs. Parkinson's disease—a critical assessment of the evidence. Eur J Neurosci 2017;45:58–66.
78. Tripathi M, Kumar A, Bal C. Neuroimaging in parkinsonian disorders. Neurol India 2018;66:S68–78.
79. Fusar-Poli P, Rubia K, Rossi G, Sartori G, Balottin U. Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. Am J Psychiatry 2012;169:264–72.
80. Bentivoglio M, Morelli M. The organization and circuits of mesencephalic dopaminergic neurons and the distribution of dopamine receptors in the brain. In: Dunnett SB, Bentivoglio M, Bjorklund A, Hokfelt T, eds. Handbook of chemical neuroanatomy: dopamine. New York: Elsevier, 2005:21–107.
81. Farley I, Price KS, Hornykiewicz O. Dopamine in the limbic regions of the human brain: normal and abnormal. Adv Biochem Psychopharmacol 1977;16:57–64.
82. Lee HM, Kwon KY, Kim M, et al. Subcortical grey matter changes in untreated, early stage Parkinson's disease without dementia. Parkinsonism Relat Disord 2014;20:622–6.

83. Mavridis IN. Nucleus accumbens and Parkinson's disease: exploring the role of Mavridis' atrophy. Open Access Case Rep 2014;3:35.
84. Nyberg EM, Tanabe J, Honce JM, et al. Morphologic changes in the mesolimbic pathway in Parkinson's disease motor subtypes. Parkinsonism Relat Disord 2015;21:536–40.
85. Arias-Carrión O, Stamelou M, Murillo-Rodríguez E, Menéndez-González M, Pöppel E. Dopaminergic reward system: a short integrative review. Int Arch Med 2010;3:24.
86. Hauser TU, Eldar E, Dolan RJ. Separate mesocortical and mesolimbic pathways encode effort and reward learning signals. Proc Natl Acad Sci U S A 2017;114:E7395–E7404.
87. Pagonabarraga J, Kulisevsky J, Strafella AP, Krack P. Apathy in Parkinson's disease. Clinical features, neural substrates, diagnosis, and treatment. Lancet Neurol 2015;14:518–31.
88. Perry DC, Kramer JH. Reward processing in neurodegenerative disease. Neurocase 2015;21:120–33.
89. Mattox ST, Valle-Inclán F, Hackley SA. Psychophysiological evidence for impaired reward anticipation in Parkinson's disease. Clin Neurophysiol 2006;117:2144–53.
90. Schott BH, Niehaus L, Wittmann BC, et al. Ageing and early-stage Parkinson's disease affect separable neural mechanisms of mesolimbic reward processing. Brain 2007;130:2412–24.
91. Sonuga-Barke EJS, Sergeant JA, Nigg J, Willcutt E. Executive dysfunction and delay aversions in attention deficit hyperactivity disorder: nosologic and diagnostic implications. Child Adolesc Psychiatr Clin N Am 2008;17:367–84.
92. Tripp G, Wickens JR. Neurobiology of ADHD. Neuropsychopharmacology 2009;57:579–89.
93. Volkow ND, Wang GJ, Newcorn JH, et al. Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. Mol Psychiatry 2011;16:1147–54.
94. Durston S, van Belle J, Zeeuw P. Differentiating frontostriatal and fronto-cerebellar circuits in attention-deficit/hyperactivity disorder. Biol Psychiatry 2011;69:1178–84.
95. Furukawa E, Bado P, Tripp G, et al. Abnormal striatal BOLD response to reward anticipation and reward delivery in ADHD. PLoS One 2014;9:e89129.
96. Hulst van BM, Zeeuw P, Bos DJ, Rijks Y, Neggers SFW, Durston S. Children with ADHD symptoms show decreased activity in ventral striatum during the anticipation of reward, irrespective of ADHD diagnosis. J Child Psychol Psychiatry 2017;58:206–14.
97. Plichta MM, Scheres A. Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. Neurosci Biobehav Rev 2014;38:125–34.
98. Getz SJ, Levin B. Cognitive and neuropsychiatric features of early Parkinson's disease. Arch Clin Neuropsychol 2017;32:769–85.
99. Harry A, Crowe SF. Is the Boston Naming Test still fit for purpose? Clin Neuropsychol 2014;28:486–504.
100. Jaeger J. Digit symbol substitution test. J Clin Psychopharmacol 2018;38:513–9.
101. Joy S, Kaplan E, Fein D. Speed and memory in the WAIS-III Digit Symbol-Coding subtest across the adult lifespan. Arch Clin Neuropsychol 2004;19:759–67.
102. Salthouse TA. What cognitive abilities are involved in trail-making performance? Intelligence 2011;39:222–32.
103. Scarpina F, Tagini S. The Stroop Color Word Test. Front Psychol 2017;8:557.
104. Shao Z, Janse E, Visser K, Meyer AS. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. Front Psychol 2014;5:1–10.
105. Elgh E, Domellöf M, Linder J, Edström M, Stenlund H, Forsgren L. Cognitive function in early Parkinson's disease: a population-based study. Eur J Neurol 2009;16:1278–84.
106. Muslimović D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 2005;65:1239–45.
107. Mostert JC, Onnink AMH, Klein M, et al. Cognitive heterogeneity in adult attention deficit/hyperactivity disorder: a systematic analysis of neuropsychological measurements. Eur Neuropsychopharmacol 2015;25:2062–74.
108. Fuermaier ABM, Aschenbrenner S, Kaunzinger I, et al. Cognitive impairment in adult ADHD—perspective matters! Neuropsychology 2015;29:45–58.
109. Fuermaier ABM, Tucha L, Koerts J, et al. Source discrimination in adults with attention deficit hyperactivity disorder. PLoS One 2013;8:e65134.
110. Rohlf H, Jucksch V, Gawrilow C, et al. Set shifting and working memory in adults with attention-deficit/hyperactivity disorder. J Neural Transm (Vienna) 2012;119:95–106.
111. Barceló F. Does the Wisconsin Card Sorting Test measure prefrontal function? Span J Psychol 2001;4:79–100.
112. Michalec J, Bezdicek O, Nikolai T, et al. A comparative study of Tower of London scoring systems and normative data. Arch Clin Neuropsychol 2017;32:328–38.
113. Nyhus E, Barceló F. The Wisconsin Card Sorting Test and cognitive assessment of prefrontal executive functions: a critical update. Brain Cogn 2009;71:437–51.
114. Litvan I, Aarsland D, Adler CH, et al. MDS task force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord 2011;26:1814–24.
115. Litvan I, Goldman JG, Tröster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society task force guidelines. Mov Disord 2012; 27:349–56.
116. LeRoy A, Jacova C, Young C. Neuropsychological performance patterns of adult ADHD subtypes. J Atten Disord 2019;23:1136–47.
117. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. Lancet 2020;395:450–62.
118. Saredakis D, Collins-Praino LE, Gutteridge DS, Stephan BCM, Keage HAD. Conversion to MCI and dementia in Parkinson's disease: a systematic review and meta-analysis. Parkinsonism Relat Disord 2019;65:20–31.
119. Henik A, Singh J, Beckley DJ, Rafal RD. Disinhibition of automatic word reading in Parkinson's disease. Cortex 1993;29: 589–99.
120. Dujardin K, Defreef JF, Rogelet P, Defebvre L, Destee A. Impairment of the supervisory attentional system in early untreated patients with Parkinson's disease. J Neurol 1999;246: 783–8.
121. Aarsland D, Brønnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease. Neurology 2009;72:1121–6.
122. Broeders M, Velseboer DC, de Bie R, et al. Cognitive change in newly-diagnosed patients with Parkinson's disease: a 5-year follow-up study. J Int Neuropsychol Soc 2013;19:695–708.
123. King JA, Colla M, Brass M, Heuser I, von Cramon D. Inefficient cognitive control in adult ADHD: evidence from trial-by-trial Stroop test and cued switching performance. Behav Brain Funct 2007;3:42.
124. Antshel KM, Faraone SV, Maglione K, et al. Executive functioning in high-IQ adults with ADHD. Psychol Med 2010;40: 1909–18.
125. Boonstra AM, Kooij JJS, Oosterlaan J, Sergeant JA, Buitelaar JK. To act or not to act, that's the problem: primarily inhibition difficulties in adult ADHD. Neuropsychology 2010; 24:209–21.
126. Kakuszi B, Tombor L, Papp S, Bitter I, Czobor P. Altered response-preparation in patients with adult ADHD: a

high-density ERP study. Psychiatry Res Neuroimaging 2016; 249:57–66.
127. Johnson DE, Epstein JN, Waid LR, Latham PK, Voronin KE, Anton RF. Neuropsychological performance deficits in adults with attention deficit/hyperactivity disorder. Arch Clin Neuropsychol 2001;16:587–604.
128. Saboya E, Coutinho G, Segenreich D, Ayrão V, Mattos P. Lack of executive functional deficits among adult ADHD individuals from a Brazilian clinical sample. Dement Neuropsychol 2009;3:34–7.
129. Pazvantoğlu O, Alptkin A, Karabekirouğlu K, et al. Neuropsychological weaknesses in adult ADHD; cognitive functions as core deficit and roles of them in persistence to adulthood. J Int Neuropsychol Soc 2012;18:819–26.
130. Butzbach M, Fuermaier ABM, Aschenbrenner S, Weisbrod M, Tucha L. Basic processes as foundations of cognitive impairment in adult ADHD. J Neural Transm (Vienna) 2019;126:1347–62.
131. Murphy P. Cognitive functioning in adults with attention-deficit/hyperactivity disorder. J Atten Disord 2002;5:203–9.
132. Kalbe E, Rehberg SP, Heber I, et al. Subtypes of mild cognitive impairment in patients with Parkinson's disease: evidence from the LANDSCAPE study. J Neurol Neurosurg Psychiatry 2016; 87:1099–105.
133. Pereira JB, Svenningsson P, Weintraub D, et al. Initial cognitive decline associated with cortical thinning in early Parkinson disease. Neurology 2014;82:2017–25.
134. Tucha O, Mecklinger L, Laufkötter R, et al. Clustering and switching on verbal and figural fluency functions in adults with attention deficit hyperactivity disorder. Cogn Neuropsychiatry 2005;10:231–48.
135. Levin BE, Llabre MM, Weiner WJ. Neuropsychological correlates of early Parkinson's disease: evidence for frontal lobe dysfunction. Ann N Y Acad Sci 1988;537:518–9.
136. Foltynie T, Brayne CEG, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 2004;127:550–60.
137. Diamond A. Executive functions. Annu Rev Psychol 2013;64: 135–68.
138. Greve KW, Williams MC, Haas WG, Littell RR, Reinoso C. The role of attention in Wisconsin Card Sorting Test performance. Arch Clin Neuropsychol 1996;11:215–22.
139. Fuermaier ABM, Tucha L, Koerts J, et al. Effects of methylphenidate on memory functions of adults with ADHD. Appl Neuropsychol Adult 2017;24:199–211.
140. Bradley V, Kapur N. Neuropsychological assessment of memory disorders. In: Gurd JM, Kischka U, Marshall JC, eds. Handbook of clinical neuropsychology. Oxford: Oxford University Press, 2010:159–83.
141. Kramer JH, Delis DC. Neuropsychological assessment of memory. In: Goldstein G, Nussbaum PD, Beers SR, eds. Neuropsychology. New York: Springer, 1998:333–56.
142. Hervey AS, Epstein JN, Curry JF. Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. Neuropsychology 2004;18:485–503.
143. Tucha L, Tucha O, Laufkötter R, Walitza S, Klein HE, Lang KW. Neuropsychological assessment of attention in adults with different sybtypes of attention-deficit/hyperactivity disorder. J Neural Transm (Vienna) 2008;115:269–78.
144. Tucha L, Fuermaier ABM, Koerts J, et al. Sustained attention in adult ADHD: time-on-task effects of various measures of attention. J Neural Transm (Vienna) 2017;124 (suppl 1):S39–53.
145. Schretlen D, Bobholz JH, Brandt J. Development and psychometric properties of the Brief Test of Attention. Clin Neuropsychol 1996;10:80–9.
146. Marchand DG, Montplaisir J, Postuma RB, Rahayel S, Gagnon J. Detecting the cognitive prodrome of dementia with Lewy bodies: a prospective study of REM sleep behavior disorder. Sleep 2017;40(1).
147. Weintraub D, Chahine LM, Hawkins KA, et al. Cognition in the course of prodromal Parkinson's disease. Mov Disord 2017;32:1640–5.
148. Bougea A, Maraki MI, Yannakoulia M, et al. Higher probability of prodromal Parkinson disease is related to lower cognitive performance. Neurology 2019;92;e2261–72.
149. Chahine LM, Weintraub D, Hawkins KA, et al. Cognition in individuals at risk for Parkinson's: Parkinson Associated Risk Syndrome (PARS) study finding. Mov Disord 2016; 31:86–94.
150. Weintraub D, Tröster AI, Marras C, Stebbins G. Initial cognitive changes in Parkinson's disease. Mov Disord 2018;33:511–9.
151. Fengler S, Liepelt-Scarfone I, Brockmann K, Schäffer E, Berg D, Kalbe E. Cognitive changes in prodromal Parkinson's disease: a review. Mov Disord 2017;32:1655–66.
152. Massicotte-Marquez J, Décary A, Gagnon JF, et al. Executive dysfunction and memory impairment in idiopathic REM sleep behavior disorder. Neurology 2008;70:1250–7.
153. Pausch C, Schomburg R, Wagenpfeil S, et al. Neuropsychological impairment in prodromal Parkinson's disease. J Neurol Sci 2016;371:117–20.
154. Ross GW, Abbott RD, Petrovitch H, Tanner CM, White LR. Pre-motor features of Parkinson's disease: the Honolulu-Asia Aging Study experience. Parkinsonism Relat Disord 2012;18 suppl 1:S199–202.
155. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–9.
156. Golomb J, Kluger A, Ferris SH. Mild cognitive impairment: historical development and summary of research. Dialogues Clin Neurosci 2004;6:351–67.
157. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–92.
158. Hoogland J, Boel JA, de Bie RMA, et al. Mild cognitive impairment as a risk factor for Parninson's disease dementia. Mov Disord 2017;32:1056–65.
159. Monastero R, Cicero CE, Baschi R, et al. Mild cognitive impairment in Parkinson's disease: the Parkinson's disease cognitive study (PACOS). J Neurol 2018;265:1050–8.
160. Santangelo C, Vitale C, Picillo M, et al. Mild cognitive impairment in newly diagnosed Parkinson's disease: a longitudinal prospective study. Parkinsonism Relat Disord 2015;21: 1219–26.
161. Weintraub D, Tröster AI, Marras C, Stebbins G. Initial cognitive changes in Parkinson's disease. Mov Disord 2018;33:511–9.
162. Yarnall AJ, Breen DP, Duncan GW, et al. Characterizing mild cognitive impairment in incident Parkinson's disease. Neurology 2014;82:308–16.
163. Callahan BL, Bierstone D, Stuss DT, Black SE. Adult ADHD: risk factor for dementia or phenotypic mimic? Front Aging Neurosci 2017;9:260.
164. Pollak J. Distinguishing between adult ADHD and mild cognitive impairment. Curr Psychiatry 2012;11:48–9.
165. Bergly TH, Sømhovd MJ. The relation between ADHD medication and mild cognitive impairment, as assessed by the Montreal Cognitive Assessment (MoCA), in patients entering substance use disorder inpatient treatment. J Dual Diagn 2018; 14:228–36.
166. Ivanchak N, Fletcher K, Jicha GA. Attention-deficit/hyperactivity disorder in older adults: prevalence and possible connections to mild cognitive impairment. Curr Psychiatry Rep 2012; 14:552–60.

167. Ivanchak N, Abner EL, Carr SA, et al. Attention-deficit/hyperactivity disorder in childhood is associated with cognitive test profiles in geriatric population but not with mild cognitive impairment or Alzheimer's disease. J Aging Res 2011;2011:1–7.
168. Tzeng N, Chung C, Lin F, et al. Risk of dementia in adults with ADHD: a nationwide, population-based cohort study in Taiwan. J Atten Disord 2019;23:995–1006.
169. Golimstok A, Rojas JI, Romano M, Zurru MC, Doctorovich D, Cristiano E. Previous adult attention-deficit and hyperactivity disorder symptoms and risk of dementia with Lewy bodies: a case-control study. Eur J Neurol 2011;18:78–84.
170. Fluegge K, Fluegge K. Antecedent ADHD, dementia, and metabolic dysregulation: a U.S. based cohort analysis. Neurochem Int 2018;112:255–8.
171. Apostolova LG, Alves G, Hwang KS, et al. Hippocampal and ventricular changes in Parkinson's disease mild cognitive impairment. Neurobiol Aging 2012;33:2113–24.
172. Brück A, Kurki T, Kaasinen V, Vahlberg T, Rinne JO. Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment. J Neurol Neurosurg Psychiatry 2004;75:1467–9.
173. Chen FX, Kang DZ, Chen FY, et al. Gray matter atrophy associated with mild cognitive impairment in Parkinson's disease. Neurosci Lett 2016;617:160–5.
174. Jia X, Wang Z, Yang T, et al. Entorhinal cortex atrophy in early, drug-naïve Parkinson's disease with mild cognitive impairment. Aging Dis 2019;10:1221–32.
175. Mak E, Williams GB, Firbank MJ, et al. Baseline and longitudinal grey matter changes in newly diagnosed Parkinson's disease: ICICLE-PD study. Brain 2015;138:2974–86.
176. Weintraub D, Doshi J, Koka D, et al. Neurodegeneration across stages of cognitive decline in Parkinson's disease. Arch Neurol 2011;68:1562–8.
177. Schultz H, Sommer T, Peters J. The role of the human entorhinal cortex in a representational account of memory. Front Hum Neurosci 2015;9:628.
178. Witter MP, Doan TP, Jacobsen B, Nilssen ES, Ohara S. Architecture of the entorhinal cortex a review of the entorhinal anatomy in rodents with some comparative notes. Front Syst Neurosci 2017;11:46.
179. Wang Z, Jia X, Chen H, Feng T, Wang H. Abnormal spontaneous brain activity in early Parkinson's disease: a resting-state fMRI study. Front Physiol 2018;9:1093.
180. Benedict RHB, DeLuca J, Phillips G, LaRocca N, Hudson LD, Rudick R; Multiple Sclerosis Outcome Assessments Consortium. Validity of the Symbol Digit Modalities Test as a cognitive performance outcome measure for multiple sclerosis. Mult Scler 2017;23:721–33.
181. Suo X, Lei D, Cheng L, et al. Multidelay multiparametric arterial spin labeling perfusion MRI and mild cognitive impairment in early stage Parkinson's disease. Hum Brain Mapp 2019;40:1317–27.
182. Argyropoulos GPD, van Dun K, Adamaszek M, et al. The cerebellar cognitive affective/Schmahmann syndrome: a task force paper. Cerebellum 2020;19:102–25.
183. Klein AP, Ulmer JL, Quinet SA, Mathews V, Mark LP. Nonmotor functions of the cerebellum: an introduction. AJNR Am J Neuroradiol 2016;37:1005–9.
184. Camicioli R, Gee M, Bouchard TP, et al. Voxel-based morphometry reveals extra-nigral atrophy patterns associated with dopamine refractory cognitive and motor impairment in parkinsonism. Parkinsonism Relat Disord 2009;15:187–95.
185. Gellersen HM, Guo CC, O'Callaghan C, Tan RH, Sami S, Hornberger M. Cerebellar atrophy in neurodegeneration—a meta-analysis. J Neurol Neurosurg Psychiatry 2017;88:780–8.
186. Ma X, Su W, Li S, et al. Cerebellar atrophy in different subtypes of Parkinson's disease. J Neurol Sci 2018;392:105–12.
187. O'Callaghan C, Hornberger M, Balsters JH, Halliday GM, Lewis SJG, Shine JM. Cerebellar atrophy in Parkinson's disease and its implication for network connectivity. Brain 2016;139:845–55.
188. Fang J, Chen H, Cao Z, et al. Impaired brain network architecture in newly diagnosed Parkinson's disease based on graph theoretical analysis. Neurosci Lett 2017:657:151–8.
189. Tuovinen N, Seppi K, de Pasquale F, et al. The reorganization of functional architecture in the early stages of Parkinson's disease. Parkinsonism Relat Disord 2018;50:61–8.
190. Duan K, Chen J, Calhoun VD, et al. Neural correlates of cognitive function and symptoms in attention-deficit/hyperactivity disorder in adults. Neuroimage Clin 2018;19:374–83.
191. Hale TS, Bookheimer S, McGough JJ, Phillips JM, McCracken JT. Atypical brain activation during simple & complex levels of processing in adult ADHD. J Atten Disord 2007;11:125–40.
192. Wolf RC, Plichta MM, Sambataro F, et al. Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder. Hum Brain Mapp 2009;30:2252–66.
193. Valera EM, Faraone SV, Biederman J, Poldrack RA, Seidman LJ. Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2005:57:439–47.
194. Valera EM, Brown A, Biederman J, et al. Sex differences in the functional neuroanatomy of working memory in adults with ADHD. Am J Psychiatry 2010;167:86–94.
195. Banich MT, Burgess GC, Dupue BE, et al. The neural basis of sustained and transient attentional control in young adults with ADHD. Neuropsychologia 2009;47:3095–104.
196. Bush G, Frazier JA, Rauch SL, et al. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. Biol Psychiatry 1999;45:1542–52.
197. Dibbets P, Evers EAT, Jolles J, Hurks PPM, Bakker K. Differential brain activation patterns in adult attention-deficit hyperactivity disorder (ADHD) associated with task switching. Neuropsychology 2010;24:413–23.
198. Schweitzer JB, Faber TL, Grafton ST, et al. Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. Am J Psychiatry 2000;157:278–80.
199. Schweitzer JB, Lee DO, Hanford RB, et al. Effect of methylphenidate on executive functioning in adults with attention-deficit/hyperactivity disorder: normalization of behavior but not related brain activity. Biol Psychiatry 2004;56:597–606.
200. Cubillo A, Halari R, Smith A, Taylor E, Rubia K. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex 2012;48:194–215.
201. Ortiz N, Parsons A, Whelan R, et al. Decreased frontal, striatal and cerebellar activation in adults with ADHD during and adaptive discounting task. Acta Neurobiol Exp (Wars) 2015;75:326–38.
202. Plichta MM, Vasic N, Wolf RC, et al. Neural hyporesponsiveness and hyperresponsiveness during immediate and delayed reward processing in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 2009;65:7–14.
203. Ernst M, Kimes AS, London ED, et al. Neural substrates of decision making in adults with attention deficit hyperactivity disorder. Am J Psychiatry 2003;160:1061–70.
204. Epstein JN, Casey BJ, Tonev ST, et al. ADHD- and medication-related brain activation effects in concordantly

affected parent-child dyads with ADHD. J Child Psychol Psychiatry 2007;48:899–913.
205. Ströhle A, Stoy M, Wrase J, et al. Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. Neuroimage 2008;39:966–72.
206. Schneider MF, Krick CM, Retz W, et al. Impairment of fronto-striatal and parietal cerebral networks correlates with attention deficit hyperactivity disorder (ADHD) psychopathology in adults—a functional magnetic resonance imaging (fMRI) study. Psychiatry Res 2010;183:75–84.
207. Alexander L, Farrelly N. Attending to adult ADHD: a review of the neurobiology behind adult ADHD. Ir J Psychol Med 2018;35:237–44.
208. Kasparek T, Theiner P, Filova A. Neurobiology of ADHD from childhood to adulthood: findings of imaging methods. J Atten Disord 2015;19:931–43.
209. Christopher L, Marras C, Duff-Canning S, et al. Combined insular and striatal dopamine dysfunction are associated with executive deficits in Parkinson's disease with mild cognitive impairment. Brain 2014;137(pt 2):565–75.
210. Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM. Clinical variables and biomarkers in the prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study. Lancet Neurol 2017;16:66–75.
211. Siepel FJ, Brønnick KS, Booij J, et al. Cognitive executive impairment and dopaminergic deficits in de novo Parkinson's disease. Mov Disord 2014;29:1802–8.
212. Brück A, Aalto S, Nurmi E, Bergman J, Rinne J. Cortical 6-[18F]fluro-L-dopa uptake and frontal cognitive functions in early Parkinson's disease. Neurobiol Aging 2005;26:891–8.
213. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain 2009;132:2958–69.
214. Badgaiyan RD, Sinha S, Sajjad M, Wack DS. Attenuated tonic and enhanced phasic release of dopamine in attention deficit hyperactivity disorder. PLoS One 2015;10:e0137326.
215. Cherkasova MV, Faridi N, Casey KF, et al. Amphetamine-induced dopamine release and neurocognitive function in treatment-naïve adults with ADHD. Neuropsychopharmacology 2014;39:1498–507.
216. Chuang W, Yeh C, Huang W, Gau SF, Shyu J, Ma K. Brain dopamine transporter availability is associated with response time (rt) variability in adults with ADHD. Neuropsychiatry (London) 2017;7:522–32.
217. Crunelle CL, Brink W, Dom G, Booij J. Dopamine transporter occupancy by methylphenidate and impulsivity in adult ADHD. Br J Psychiatry 2014;204:486–7.
218. Volkow ND, Wang G-J, Kollins SH, et al. Evaluating dopamine reward pathway in ADHD: clinical implications. JAMA 2009;302:1084–91.
219. Baiano C, Barone P, Trojano L, Santangelo G. Prevalence and clinical aspects of mild cognitive impairment in Parkinson's disease: a meta-analysis. Mov Disord 2020;35:45–54.
220. Costa A, Peppe A, Zabberoni S, Scalici F, Caltagirone C, Carlesimo GA. Apathy in individuals with Parkinson's disease associated with mild cognitive impairment. A neuropsychological investigation. Neuropsychologia 2018;118:4–11.
221. Ravina B, Elm J, Camicioli R, et al. The course of depressive symptoms in early Parkinson's disease. Mov Disord 2009; 24:1306–11.
222. Jones JD, Mangal P, Lafo J, Okunm MS, Bowers D. Mood differences among Parkinson's disease patients with mild cognitive impairment. J Neuropsychiatry Clin Neurosci 2016; 28:211–6.
223. den Brok MGHE, van Dalen JW, van Gool WA, Moll van Charante EP, de Bie RM, Richard E. Apathy in Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2015;30:759–69.
224. Fang F, Xu Q, Park Y, et al. Depression and the subsequent risk of Parkinson's disease in the NIH-AARP Diet and Health Study. Mov Disord 2010;25:1157–62.
225. O'Sullivan SS, Williams DR, Gallagher DA, Massey LA, Silveira-Moriyama L, Lees AJ. Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. Mov Disord 2007;23:101–6.
226. Shiba M, Bower JH, Maraganore DM, et al. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. Mov Disord 2000;15:669–77.
227. Darweesh SKL, Verlinden VJA, Stricker BH, Hofman A, Koudstaal PJ, Ikram A. Trajectories of prediagnostic functioning in Parkinson's disease. Brain 2017;140;429–41.
228. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol 2015;14:5764.
229. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord 2015;30:1600–9.
230. Ehmann TS, Beninger RJ, Gawel Mj, Riopelle RJ. Depressive symptoms in Parkinson's disease: a comparison with disabled control subjects. J Geriatr Psychiatry Neurol 1990;3:3–9.
231. Kano O, Ikeda K, Cridebring D, Takazawa T, Yoshii Y, Iwasaki Y. Neurobiology of depression and anxiety in Parkinson's disease. Parkinsons Dis 2011;2011:143547.
232. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry 2006;163:716–23.
233. Meinzer M, Lewinsohn PM, Pettit JW, et al. Attention deficit-hyperactivity disorder in adolescence predicts onset of major depressive disorder through early adulthood. Depress Anxiety 2013;30:546–53.
234. Sobanski E, Brüggemann D, Alm B, et al. Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 2007;257:371–7.
235. Torgersen T, Gjervan B, Rasmussen K. ADHD in adults: a study of clinical characteristics, impairment and comorbidity. Nord J Psychiatry 2006;60:38–43.
236. Farone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. Mol Psychiatry 2019;24:562–75.
237. Humphreys KL, Katz SJ, Lee SS, Hammen CL, Brennan A, Najman JM. The association of ADHD and depression: mediation by peer problems and parent-child difficulty in two complementary samples. J Abnorm Psychol 2013;122:854–67.
238. Knouse LE, Zvorsky I, Safren SA. Depression in adults with attention-deficit/hyperactivity disorder (ADHD): the mediating role of cognitive-behavioral factors. Cognit Ther Res 2013;37:1220–32.
239. Powell V, Riglin L, Hammerton G, et al. What explains the link between childhood ADHD and adolescent depression? Investigating the role of peer relationships and academic attainment. Eur Child Adolesc Psychiatry 2020;29:1581–91.
240. Riglin L, Leppert B, Dardaini C, et al. ADHD and depression: investigating a causal explanation. Psychol Med 2020 Apr 6 [Epub ahead of print].
241. Baumeister AA. Could clinical use of stimulant medications increase risk for Parkinson's disease or other neurological sequelae? A review of the evidence. J Pharmacol Clin Res 2017;3: 555618.
242. Thrash B, Thiruchelvan K, Ahuja M, Suppiramaniam V, Dhanasekaran M. Methamphetamine-induced neurotoxicity: the road to Parkinson's disease. Pharmacol Rep 2009;61: 966–77.

243. Ares-Santos S, Granado N, Espadas I, Matrinez-Murillo R, Moratalla R. Methamphetamine causes degeneration of dopamine cell bodies and terminals of the nigrostriatal pathway evidenced by silver staining. Neuropsychopharmacology 2014; 39:1066–80.
244. Harvey DC, Laćan G, Tanious SP, Melega WP. Recovery from methamphetamine induced long-term nigrostriatal dopaminergic deficits without substantia nigra cell loss. Brain Res 2000; 871:259–70.
245. Sonsalla PK, Jochnowitz ND, Zeevalk GD, Oostveen JA, Hall ED. Treatment of mice with methamphetamine produces cell loss in the substantia nigra. Brain Res 1996;738:172–5.
246. Bowyer JF, Schmued LC. Fluro-ruby labeling prior to an amphetamine neurotoxic insult shows a definitive massive loss of dopaminergic terminals and axons in the caudate-putamen. Brain Res 2006;1075:236–9.
247. Ricaurte GA, Seiden LS, Schuster CR. Further evidence that amphetamines produce long-lasting dopamine neurochemical deficits by destroying dopamine nerve fibers. Brain Res 1984; 303:359–64.
248. Ricaurte GA, Mechan AO, Yuan J, et al. Amphetamine treatment similar to that used in the treatment of adult attention-deficit/hyperactivity disorder damages dopaminergic nerve endings in the striatum of adult nonhuman primates. J Pharmacol Exp Ther 2005;315:91–8.
249. Fricks-Gleason AN, German CL, Hoonakker AJ, et al. An acute, epitope-specific modification in the dopamine transporter associated with methamphetamine-induced neurotoxicity. Synapse 2016;70:139–46.
250. Harvey DC, Laćan G, Melega WP. Regional heterogeneity of dopaminergic deficits in vervet monkey striatum and substantia nigra after methamphetamine exposure. Exp Brain Res 2000; 133:349–58.
251. McFadden LM, Vieira-Brock PL, Hanson GR, Fleckenstein AE. Prior methamphetamine self-administration attenuates the dopaminergic deficits caused by a subsequent methamphetamine exposure. Neuropharmacology 2015;93:146–54.
252. Melega WP, Jorgensen MJ, Laćan G, et al. Long-term methamphetamine administration in the vervet monkey models aspects of a human exposure: Brain neurotoxicity and behavioral profiles. Neuropsychopharmacology 2008;33:1441–52.
253. Ryan LJ, Linder JC, Martone ME, Groves PM. Histological and ultrastructural evidence that d-amphetamine causes degeneration in neostriatum and frontal cortex of rats. Brain Res 1990;518:67–77.
254. Wagner GC, Ricaurte GA, Johanson CE, Schuster CR, Seiden LS. Amphetamine induces depletion of dopamine and loss of dopamine uptake sites in caudate. Neurology 1980;30: 547–50.
255. Yuan J, McCann U, Ricaurte G. Methylphenidate and brain neurotoxicity. Brain Res 1997;767:172–5.
256. Zhang L, Kitaichi K, Fujimoto Y, et al. Protective effects of minocycline on behavioral changes and neurotoxicity in mice after administration of methamphetamine. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1381–93.
257. Woolverton WL, Ricaurte GA, Forno LS, Seiden LS. Long-term effects of chronic methamphetamine administration in rhesus monkeys. Brain Res 1989;486:73–8.
258. Rumpf JJ, Albers J, Fricke C, Mueller W, Classen J. Structural abnormality of substantia nigra induced by methamphetamine abuse. Mov Disord 2017;32:1784–8.
259. Todd G, Noyes C, Flavel SC, et al. Illicit stimulant use is associated with abnormal substantia nigra morphology in humans. PLoS One 2013;8:e56438.
260. Todd G, Pearson-Dennett V, Wilcox RA, et al. Adults with a history of illicit amphetamine use exhibit abnormal substantia nigra morphology and parkinsonism. Parkinsonism Relat Disord 2016;25:27–32.
261. Kitamura O. Detection of methamphetamine neurotoxicity in forensic autopsy cases. J Legal Med 2009;11:S63–5.
262. Moszczynska A, Fitzmaurice P, Ang L, et al. Why is parkinsonism not a feature of human methamphetamine users? Brain 2004;127:363–70.
263. Wilson JM, Kalasinsky KS, Levey AI, et al. Striatal dopamine nerve terminal and markers in human, chronic methamphetamine users. Nat Med 1996;2:699–703.
264. McCann UD, Kuwabara H, Kumar A, et al. Persistent cognitive and dopamine transporter deficits in abstinent methamphetamine users. Synapse 2008;62:91–100.
265. McCann UD, Wong DF, Yokoi F, Villemagne V, Dannals RF, Ricaurte GA. Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C] WIN-35,428. J Neurosci 1998;18:8417–22.
266. Volkow ND, Chang L, Wang GJ, et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am J Psychiatry 2001;158:377–82.
267. Volkow ND, Chang L, Wang GJ, et al. (2001). Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. J Neurosci 2001;21:9414–8.
268. Callaghan RC, Cunningham JK, Sykes J, Kish SJ. Increased risk of Parkinson's disease in individuals hospitalized with conditions related to the use of methamphetamine or other amphetamine-type drugs. Drug Alcohol Depend 2012;120:35–40.
269. Christine CW, Garwood ER, Schrock LE, Austin DE, McCulloch CE. Parkinsonism in patients with history of amphetamine exposure. Mov Disord 2010;25:228–31.
270. Curtin K, Fleckenstein AE, Robison RJ, Crookston MJ, Smith KR, Hanson GR. Methamphetamine/amphetamine abuse and risk of Parkinson's disease in Utah: a population-based assessment. Drug Alcohol Depend 2015;146:30–8.
271. Garwood ER, Bekele W, McCulloch CE, Christine CW. Amphetamine exposure is elevated in Parkinson's disease. Neurotoxicology 2006;27:1003–6.
272. Lappin JM, Darke S, Farrell M. Methamphetamine use and future risk for Parkinson's disease: evidence and clinical implications. Drug Alcohol Depend 2018;187:134–40.
273. Tripathi R, Saber H, Chauhan V, Tripathi K, Factor S. Parkinson disease from long term drug abuse: meta-analysis of amphetamine/methamphetamine and Parkinson disease. Neurology 2018;90(suppl 15).
274. Ludolph AG, Schaz U, Storch A, Liebau S, Fegert JM, Boeckers TM. Methylphenidate exerts no neurotoxic effect, but neuroprotective effects in vitro. J Neural Transm (Vienna) 2006;113:1927–34.
275. Zaczek R, Battaglia G, Contrera JF, Culp S, DeSouza EB. Methylphenidate and pemoline do not cause depletion of rat brain monoamine markers similar to that observed with methamphetamine. Toxicol Appl Pharmacol 1989;100:227–33.
276. Sadasivan S, Pond BB, Pani AK, Qu C, Jiao Y, Smeyne RJ. Methylphenidate exposure induces dopamine neuron loss and activation of microglia in the basal ganglia of mice. PLoS One 2012;7:e33693.
277. Moll GH, Hause SA, Rüther E, Rothenberger A, Huether G. Early methylphenidate administration to young rats causes a persistent reduction in the density of striatal dopamine transporters. J Child Adolesc Psychopharmacol 2001;11:15–24.
278. Gill KE, Pierre PJ, Daunais J, et al. Chronic treatment with extended release methylphenidate does not alter dopamine systems or increase vulnerability for cocaine self-administration: a study in nonhuman primates. Neuropsychopharmacology 2012;37:2555–65.

279. Soto PL, Wilcox KM, Zhou Y, et al. Long-term exposure to oral methylphenidate or dl-amphetamine mixture in peri-adolescent rhesus monkeys: effects on physiology, behavior, and dopamine system development. Neuropsychopharmacology 2012; 37:2566–79.
280. Comim CM, Gomes KM, Réus GZ, et al. Methylphenidate treatment causes oxidative stress and alters energetic metabolism in an animal model of attention-deficit hyperactivity disorder. Acta Neuropsychiatr 2014;26:96–103.
281. Schmitz F, Pierozan P, Rodrigues AF, et al. Chronic treatment with a clinically relevant dose of methylphenidate increases glutamate levels in cerebrospinal fluid and impairs glutaminergic homeostasis in prefrontal cortex of juvenile rats. Mol Neurobiol 2016;53:2384–96.
282. Tung C, Chang S, Huang C, Huang N. The neurotoxic mechanisms of amphetamine: step by step for striatal dopamine depletion. Neurosci Lett 2017;639:185–91.
283. Kakish J, Lee D, Lee JS. Drugs that bind to α-synuclein: neuroprotective or neurotoxic? ACS Chem Neurosci 2015;6:1930–40.
284. Hales CM, Kit BK, Gu Q, Ogden CL. Trends in prescription medication use among children and adolescents—United States, 1999–2014. JAMA 2018;319:2009–20.
285. Piper BJ, Ogden CL, Simoyan OM, et al. Trends in use of prescription stimulants in the United States and territories, 2006 to 2016. PLoS One 2018;13:e0206100.
286. Bachmann CJ, Wijlaars LP, Kalverdijk LJ, et al. Trends in ADHD medication use in children and adolescents in five Western countries, 2005–2012. Eur Neuropsychopharmacol 2017;27:484–93.
287. Raman SR, Man KKC, Bahmanyar S, et al. Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. Lancet Psychiatry 2019;5:824–35.
288. Compton WM, Han B, Blanco C, Johnson K, Jones CM. Prevalence and correlates of prescription stimulant use, misuse, use disorders, and motivations for misuse among adults in the United States. Am J Psychiatry 2018;175:741–55.
289. Adeyemo BO, Biderman J, Zafonte R, et al. Mild traumatic brain injury and ADHD: a systematic review of the literature and meta-analysis. J Atten Disord 2014;18:576–84.
290. Gardner RC, Burke JF, Nettiksimmons J, Goldman S, Tanner CM, Yaffe K. Traumatic brain injury in later life increases risk for Parkinson's disease. Ann Neurol 2015;77:987–95.
291. Bjørklund G, Stejskal V, Urbina MA, Dadar M, Chirumbolo S, Mutter J. Metals and Parkinson's disease: mechanisms and biochemical processes. Curr Med Chem 2018;25:2198–214.
292. Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG. Attention deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides in U.S. children 8–15 years. Pediatrics 2010;125:e1270–7.
293. Brouwer M, Huss A, van der Mark M, et al. (2017). Environmental exposure to pesticides and the risk of Parkinson's disease in the Netherlands. Environ Int 2017;107:100–10.
294. Froehlich TE, Lanphear BP, Auinger P, et al. Association of tobacco and lead exposures with attention-deficit/hyperactivity disorder. Pediatrics 2009;124:e1054–63.
295. Sagiv SK, Thurston SW, Bellinger DC, Amarasiriwardena C, Korrick SA. Prenatal exposure to mercury and fish consumption during pregnancy and ADHD-related behavior in children. Arch Pediatr Adolesc Med 2012;166:1123–31.
296. Weisskopf MG, Weuve J, Nie H, et al. Association of cumulative lead exposure with Parkinson's disease. Environ Health Perspect 2010;118:1609–13.
297. Geissler JM, International Parkinson Disease Genomics Consortium members, Romanos M, Gerlach M, Berg D, Schulte C. No genetic association between attention-deficit/hyperactivity disorder (ADHD) and Parkinson's disease in nine ADHD candidate SNPs. Atten Defic Hyperact Disord 2017;9:121–7.
298. Jarick I, Volckmar A-L, Pütter C, et al. Genome-wide analysis of rare copy number variations reveals PARK2 as a candidate gene for attention-deficit/hyperactivity disorder. Mol Psychiatry 2014;19:115–21.
299. Dawson TM, Dawson Vl. The role of parkin in familial and sporadic Parkinson's disease. Mov Disord 2010;25:S32–9.
300. Outeiro TF, Koss DJ, Erskine D, et al. Dementia with Lewy bodies: an update and outlook. Mol Neurodegener 2019;14:5.
301. Surgucheva I, He S, Rich MC, et al. Role of synucleins in traumatic brain injury—an experimental in vitro and in vivo study in mice. Mol Cell Neurosci 2014;63:114–23.
302. Uryu K, Giasson BI, Longhi L, et al. Age-dependent synuclein pathology following traumatic brain injury in mice. Exp Neurol 2003;184:214–24.
303. Rokad D, Ghaisas S, Harischandra DS, et al. Role of neurotoxicants and traumatic brain injury in α-synuclein protein misfolding and aggregation. Brain Res Bull 2017;133:60–70.
304. Noyes K, Liu H, Holloway R, Dick AW. Accuracy of Medicare claims data in identifying Parkinsonism cases: comparison with the Medicare current beneficiary survey. Mov Disord 2007;22:509–14.
305. Asherson P, Agnew-Blais J. Annual research review: does late-onset attention-deficit/hyperactivity exist? J Child Psychol Psychiatry 2019;60:333–52.