DOI 10.1007/s00702-004-0168-1
J Neural Transm (2004) 111: 1303–1315

Journal of Neural Transmission
Printed in Austria

Cognitive dysfunction and dementia in Parkinson's disease

J. L. W. Bosboom[1], **D. Stoffers**[1,2], and **E. Ch. Wolters**[1]

[1] Research Institute Neurosciences Vrije Universiteit, Department of Neurology, VU University Medical Center, and
[2] Department of Clinical Neuropsychology, VU University, Amsterdam, The Netherlands

Received April 2, 2004; accepted May 8, 2004
Published online June 30, 2004;

Summary. Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder mainly characterized by degeneration of dopaminergic neurons in the substantia nigra and the ventral tegmental area, in combination with a varying loss of central noradrenergic (locus coeruleus), cholinergic (nucleus basalis of Meynert) and serotonergic (dorsal raphe nuclei) integrity, leading to a multitude of motor and non-motor behavioral disturbances.

Apart from the clinical motor hallmarks, in the early stages of disease, subtle cognitive dysfunction might be seen comprising mainly executive dysfunction, with secondary visuospatial and mnemonic disturbances. In about 20–40% of patients, these problems may eventually proceed to dementia, which constitutes an important risk factor for caregiver distress, decreased quality of life and nursing home placement. Dementia in PD is typically characterized by a progressive dysexecutive syndrome with attentional deficits and fluctuating cognition, often accompanied by psychotic symptoms. It is thought to be the result of a combination of both subcortical and cortical changes. PD-related dopaminergic deficiency in the nucleus caudatus and mesocortical areas (due to degeneration of projections from the substantia nigra and ventral tegmental area) and cholinergic deficiency in the cortex (due to degeneration of ascending projections from the nucleus basalis of Meynert), combined with additional Alzheimer-pathology and cortical Lewy bodies, may greatly contribute to dementia.

Current treatment of dementia in PD is based on compensation of the profound cholinergic deficiency. Recent studies with the cholinesterase inhibitors galantamine, donepezil and rivastigmine show promising results in improving cognition and ameliorating psychotic symptoms, which must further be confirmed in randomized controlled trials.

Keywords: Parkinson's disease, cognition, dementia.

Introduction

Parkinson's disease is a slowly progressive neurodegenerative disease, in which dopaminergic neurons in the substantia nigra and the ventral tegmental area degenerate, leading to dopaminergic deficiency in the striatum and mesocorticolimbic areas. In addition to degeneration of the dopaminergic system, in PD other ascending subcortical neurotransmitter systems are affected as well: the cholinergic system (nucleus basalis of Meynert), the noradrenergic system (locus coeruleus) and serotonergic system (dorsal raphe nuclei) (Jellinger, 1999). The cardinal motor symptoms are brady(hypo-)kinesia, tremor, rigidity and postural instability. Non-motor symptoms mainly comprise autonomic disturbances, depression, cognitive dysfunction/dementia and psychotic symptoms. As a rule, these symptoms are often more important in determining the quality of life of patients and caregivers than the motor disturbances.

Dementia in PD constitutes not only an important factor for caregiver distress and nursing home placement (Aarsland, 2000, 1999), but is also associated with increased mortality (independent of severity of motor symptoms) (Levy, 2000). As these symptoms are potentially treatable, identification is of major clinical importance both for the patients and their caregivers and may enable the Parkinson's disease patient to maintain living at home for a longer period. Additionally, postponement of nursing home placement can lead to substantial reductions in healthcare costs.

Cognitive deficits in non-demented PD patients

Cognitive impairment is often associated with PD, although deficits may be relatively subtle and not clinically apparent, or not overtly affect daily functioning. However, when compared to controls, subtle to prominent cognitive impairment is almost always found in PD patients. A wide variety of cognitive deficits has been described in non-demented PD patients, the most prominent of which is a deficit in executive function.

Executive function is a broad term used to describe a range of cognitive functions involved in the realisations of goal-directed, adaptive behaviour in response to new, challenging environmental situations, including attention, inhibition, task management, planning, monitoring and coding (Smith, 1999). A dysexecutive syndrome, resembling cognitive deficits found in frontal lobe patients (Rowe, 2002; Rogers, 1998a), is thought to be at the heart of cognitive dysfunction and dementia in PD and is usually one of the earliest cognitive symptoms found in PD (Dubois, 1997).

Besides executive dysfunction, there is considerable evidence of deficits in *visuospatial function* in non-demented PD, even when tests contain few motor components (Hovestadt, 1987; Boller, 1984; Bowen, 1972). Most authors, however, believe visuospatial dysfunction to be the result of the high cognitive demand that is usually required by such tasks. Indeed, with the possible exception of judgment of line orientation, it would appear that visuospatial dysfunction in PD can be readily explained by the demand of visuospatial tasks on executive functions such as planning and (shifting of) attention (Bondi, 1993; Raskin, 1992; Ogden, 1990; Ransmayr, 1987; Brown, 1986).

Mnemonic dysfunction has also frequently been reported in PD. The most consistent findings in patients with PD are deficits of working memory (Owen, 1993; Cooper, 1993, 1992; Bradley, 1989; Wilson, 1980) and explicit memory (Buytenhuijs, 1994; Taylor, 1990, 1986). Working memory can be defined as the ability to hold internal representations in short-term memory and to manipulate this mnemonic information on line to enable adaptive behaviour to be based on these representations rather than on immediate stimuli (Goldman-Rakic, 1987). Most studies find preserved short-term memory in non-demented PD (Owen, 1997). The executive processes that operate on the contents of this memory, however, are often impaired (Pillon, 1998). Therefore, most deficits in working memory can probably also be explained in terms of executive dysfunction. Defective explicit memory in PD can largely be remedied by semantic cueing or probing (Scheltens, 1999; Pillon, 1993). This suggests that although new information is stored, it is not readily accessed, pointing to defective usage of stored information. In conclusion, quite analogous to visuospatial function, mnemonic function would for the most part be secondarily impaired, due to the reliance of its manifestation on executive functionality.

Several studies have also shown bradyphrenia in PD (Cooper, 1994; Mayeux, 1987), although this is still a matter of much controversy in the literature. It has been suggested that the finding of reduced cognitive speed may very well have been caused by the inclusion of patients with mild dementia or depression (Smith, 1998). For an excellent and comprehensive review of the literature on cognitive deficits in PD, one is advised to read the chapter by Pillon and co-workers in the recent Handbook of Neuropsychology (Pillon, 2001).

Dementia in PD

The aforementioned cognitive deficits may eventually proceed to dementia in a number of patients. Prevalence and incidence vary considerably among studies, possibly due to differences in patient population, study design and criteria for diagnosing PD and dementia. In cross-sectional studies, prevalence of dementia in PD ranges from 10% to over 40% (Aarsland, 1996; Mayeux, 1988, 1992). Features associated with prevalence of dementia include age (Aarsland, 1996; Mayeux, 1988), age at onset of PD (Aarsland, 1996; Mayeux, 1988, 1992), disease severity (Mayeux, 1988), disease duration (Aarsland, 1996), depression (Aarsland, 1996) and presence of atypical parkinsonian symptoms (Aarsland, 1996). The association with older age is of particular strength.

Prospective studies have reported a cumulative incidence of 19 to 53% (the follow up period varied in these studies) (Read, 2001; Levy, 2000; Hughes, 2000; Marder, 1995). Recently, in a prospective study with 8 years follow-up, 78.2% of patients eventually developed dementia (Aarsland, 2003a). Incidence rates vary from 31.4 to 122.5 cases per 1000 person years (Aarsland, 1996, 2003a; Read, 2001; Hughes, 2000; Mahieux, 1998; Mayeux, 1990) and the risk for developing dementia in PD-patients is up to six times higher compared to age-matched control subjects (Aarsland, 2001).

In these studies, factors associated with the risk of dementia were found to be age (Levy, 2002; Aarsland, 2001; Read, 2001; Stern, 1993), age at onset of PD (Mahieux, 1998), disease severity (Aarsland, 2001; Hughes, 2000; Marder, 1995; Elizan, 1986), age at entry in the study (Read, 2001; Hughes, 2000), confusional state (Stern, 1993; Elizan, 1986), early hallucinations and the mixed tremor/akinetic form of PD (Aarsland, 2003a).

The neuropsychological profile of PD-related dementia is characterized by a progressive dysexecutive syndrome, as described earlier. Essentially, the same types of deficits are found in non-demented patients (Girotti, 1988), but are more severe in demented patients. From this perspective, it is not surprising that several recent studies have pointed to the predictive value of prodromal impairment of verbal memory (immediate and delayed recall) and especially executive function (Woods, 2003; Levy, 2002; Jacobs, 1995).

Memory deficits are present, but are less severe compared to AD (Aarsland, 2003c). Moreover, the quality of memory impairment differs from that seen in AD. In both conditions it is characterized by a deficit in free recall, but in PDD, as mentioned before, this can often be corrected by semantic cueing (Scheltens, 1999). Therefore, in PDD the problem seems to be of retrieval, and not of encoding. Indeed, recognition memory is often well preserved in demented PD-patients.

Unlike in AD, instrumental disorders such as aphasia, apraxia or agnosia are not very common in PDD (Dubois, 1997; Huber, 1989).

Psychotic symptoms however, are especially common in PDD. Hallucinations (sensory percepts in the absence of an external stimulus (American Psychiatric Association, 1994)), mainly visual, are the most frequent symptom. These are mostly non-threatening and often consist of vivid, colourful and sometimes fragmented figures of beloved (deceased) familiar persons and/or animals, which are described in detail (Poewe, 2003). Insight is retained in the majority of occasions, but with reality testing deteriorating, the hallucinations may change and become more frightening, possibly inducing anxiety and panic attacks (Wolters, 2001). Loss of insight is particularly seen in demented patients (Fenelon, 2000). Delusions (false beliefs based on incorrect inference about external reality (American Psychiatric Association, 1994)) are less common than hallucinations and mainly of the paranoid type, dealing with persecution, spousal infidelity or jealousy (Bosboom, 2004).

Attentional deficits and fluctuating cognition are also very common in PDD. These features, together with parkinsonism and the above mentioned visual hallucinations, are the main characteristics of dementia with Lewy bodies (DLB), possibly accounting for 15–20% of the dementias (McKeith, 1996). Indeed, PDD and DLB share many clinical (Ballard, 2002; Connor, 1998; Dubois, 1997) and pathological (Harding, 2001) features and are often difficult to distinguish other than by the temporary onset of dementia and psychosis in relation to parkinsonism (Richard, 2002). Therefore, Parkinson's disease and dementia with Lewy bodies are often considered to be part of the same disease spectrum (Burn, 2003a; Ballard, 2000; McKeith, 2000b), although this matter is still under considerable debate (Litvan, 1998). It is suggested that similar pathological mechanisms may underlie the clinical symptoms, including dementia and psychotic symptoms.

Pathophysiology of cognitive deficits and dementia in PD

Based on his work in primates, Alexander described five parallel, segregated circuits interconnecting well-defined subregions of the basal ganglia to particular cortical fields via the thalamus (Alexander, 1986). Disruptions at either basal ganglia or cortical points in such a circuit have been shown to produce similar behavioural effects (Cummings, 1993). In one of the five circuits, the so-called dorsolateral prefrontal loop which is thought to be involved in executive behaviour, the dorsolateral part of the prefrontal cortex projects to the caudate nucleus. Hence projections lead trough pallidum and thalamus back to the prefrontal cortex. It may therefore well be that degeneration of the dopaminergic nigrostriatal pathway affects executive function by causing a disruption at the level of the caudate nucleus, a notion supported by findings from imaging studies (Lewis, 2004; Owen, 1998). This notion is further underlined by the fact that dopamine depletion in PD is greatest in the caudate's most rostral portion, exactly the part that is most heavily interconnected to the dorsolateral region of the prefrontal cortex.

Alternatively, cognitive dysfunction in non-demented PD could be caused by dopamine depletion in the frontal cortex itself, resulting from degeneration of the mesocortical dopaminergic system mainly projecting from the ventral tegmental area. In any case, the exact contribution of dopaminergic deficiency to cognitive defects in Parkinson's disease remains controversial, largely because the cognitive effects of dopaminomimetics appear heterogeneous. While some studies point to a positive effect on executive function (Lange, 1992, 1995), (working)memory and attention (Bowen, 1975), others actually find deleterious effects, especially in the executive domain (Gotham, 1988) or show no effects at all. A recent longitudinal study showed the beneficial effect of dopaminergic medication to be particularly prominent in the very early stages of disease (Kulisevsky, 2000b) (for a review of the pertinent literature, read (Kulisevsky et al., 2000a)). Also, cognitive function in PD seems to correlate with motor symptoms that show little response to dopaminergic treatment (axial symptoms and gait disturbances), but not with levodopa-responsive symptoms (akinesia and rigidity) (Burn, 2003b; Levy, 2000; Pillon, 1989).

In conclusion, it would appear that dopaminergic medication improves or impairs cognitive performance depending on both the nature of the task and the basal level of DA function in underlying nigrostriatal and mesocortical circuitry.

The exact pathophysiology of dementia in PD is uncertain. A number of neuropathological and neurochemical changes in PD are thought to be involved.

The aforementioned deterioration of the dopaminergic system is likely to contribute to the progression of cognitive deficits into more overt dementia. This is supported by the association between dementia and the loss of dopaminergic neurons in the medial part of the substantia nigra (Paulus, 1991; Rinne, 1989), projecting to the nucleus caudatus and mesocortical and mesolimbic areas, and in the ventral tegmental area, with ascending dopaminergic projections to mesocortical and mesolimbic areas (Oades, 1987; Thierry, 1978).

Still, dopaminergic deficiency by itself is not considered sufficient for the development of dementia. Non-dopaminergic systems are likely to be involved as well. As already mentioned, several neuromodulatory systems are affected to varying degree in PD, mainly the serotonergic, noradrenergic and cholinergic systems (Jellinger, 1999).

Neuronal loss in locus coeruleus (LC) and noradrenergic deficiency in the cortex were reported to be associated with dementia in PD (Cash, 1987). However, in other studies, this relationship could not be found (Paulus, 1991; Chan-Palay, 1989). Loss of serotonergic neurons in the dorsal raphe nucleus (DRN) has mainly been associated with depression, but demented and non-demented patients did not differ on neuronal counts in this area (Paulus, 1991; Scatton, 1983).

Furthermore, Perry et al. (1991) could not establish a correlation between dementia in PD and diminished monoaminergic activity. Instead, they reported an association between cholinergic deficiency and dementia. Indeed, not only in Alzheimer's disease (Francis, 1999; Davies, 1976), but especially in PDD and DLB, a cholinergic deficit has been implicated in the pathophysiology of cognitive impairment. In these patients, a definite and more pronounced depletion of cholinergic neurons is found in the nucleus basalis of Meynert compared to AD-patients and non-demented patients (Perry, 1985; Whitehouse, 1983), together with diminished cholinergic activity in the cortex (Ballard, 2002; Mattila, 2001; Tiraboschi, 2000; Perry, 1991). This nucleus in the basal forebrain, consisting for 90% of cholinergic neurons, provides major cholinergic projections to the amygdale and neocortex (Perry, 1985; Whitehouse, 1983; Mesulam, 1983a, b). The cholinergic deficit, possibly superposed on a normal age-related deterioration of the cholinergic system (Perry, 1992), is strongly correlated with cognitive impairment in both conditions (Mattila, 2001; Kuhl, 1996; Perry, 1985) and therefore, is likely to constitute an important mechanism in the development of dementia.

This is further supported by the propensity of anticholinergic agents to elicit cognitive dysfunction in PD-patients (Bedard, 1999; de Smet, 1982) and the clinical beneficial results of cholinesterase inhibitors in disorders with associated dementia (see later).

Beside these subcortical neuropathological changes in PDD, important cortical changes have been implicated in the etiology of dementia in PD. AD-pathology, especially AD-neurites, are more abundant in demented patients compared to non-demented PD-patients, correlating with the severity of PDD in a number of studies (Jellinger, 2002; de Vos, 1995), though other authors point to the importance of cortical LB's as a neuropathological substrate for dementia in PD (Apaydin, 2002; Harding, 2001; Hurtig, 2000; Mattila, 2000), independent of AD-pathology (Hurtig, 2000; Mattila, 1998, 2000). This, however, is opposed by authors reporting comparable cortical LB distribution in demented and non-demented PD-patients (Richard, 2002; SantaCruz, 1999; de Vos, 1995). Thus, this matter is still under considerable debate.

Overall, dementia in PD is thought to be the result of a combination of several subcortical and cortical pathological changes. Subcortical mechanisms include both dopaminergic deficiency in the nucleus caudatus and mesocortical

areas, causing executive dysfunction, and cortical cholinergic deficiency, mainly due to degeneration of the nucleus basalis of Meynert. The latter may further deteriorate the patient's executive functions by inducing attentional deficits (possibly together with noradrenergic deficiency). This effect might be increased by ageing. Additional AD-like changes and the presence of Lewy bodies in the cortex are likely to further compromise cognitive functions, with development of dementia as soon as a certain threshold is reached (Wolters, 1998).

Treatment of dementia in PD

Current pharmacological intervention in dementia is symptomatic and is based on compensation for the profound loss of cholinergic activity in the cortex. In AD, modest beneficial results have been reported with the cholinesterase inhibitors galantamine, rivastigmine and donepezil (Gabelli, 2003; Tariot, 2000; Cummings, 1998; Rogers, 1998b). These compounds might even prove to be more effective in PDD (and DLB) for several reasons. First, as mentioned above, the deterioration of ascending cholinergic projections from the nucleus basalis of Meynert is probably more pronounced in PDD and DLB compared to AD (Perry, 1985; Whitehouse, 1983). Second, the cortex is thought to be relatively spared in PDD (Perry, 1993).

An early study with tacrine in PD reported a definite amelioration of psychotic behaviour (Hutchinson, 1996), but this compound has been withdrawn from the market because of hepatotoxicity.

Galantamine and donepezil are cholinesterase inhibitors that stimulate the nicotinic receptor (Samochocki, 2000). In open label studies with these compounds, cognition as well as hallucinations improved in PD-patients with dementia without significant worsening of extrapyramidal features (Aarsland, 2003b; Bergman, 2002; Fabbrini, 2002; Werber, 2001).

Open label studies with rivastigmine, a dual acetyl and butyryl cholinesterase inhibitor have yielded similar results in PDD as well as DLB (Giladi, 2003; Bullock, 2002; Grace, 2001; Reading, 2001; McKeith, 2000a, c). In these studies, extrapyramidal features did not worsen significantly and even tended to improve in one (Reading, 2001) and worsened after withdrawal of rivastigmine in another (McKeith, 2000c). Given the possible parkinsonism inducing effects of cholinergic drugs, the improvement as seen in the motor scores of the Parkinson's disease patients treated with cholinesterase inhibitors is unexpected. In our own (unpublished) experience rivastigmine only tends to increase tremor in demented PD-patients.

The only randomized controlled trial with cholinesterase inhibitors in PDD so far, has been conducted with donepezil. The same beneficial results as in the previous open label studies have been reported, though the number of patients was small (Aarsland, 2002). A large, randomized, placebo controlled trial with rivastigmine in PDD, is currently being conducted.

The most frequent side effects reported with the use of cholinesterase inhibitors are nausea, vomiting and anorexia, sometimes causing problems with drug titration. Therefore, the drugs should be started at low dose with a gradual increase to the maximum tolerated dose.

References

Aarsland D, Tandberg E, Larsen JP, Cummings JL (1996) Frequency of dementia in Parkinson disease. Arch Neurol 53: 538–542

Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E (1999) Mental symptoms in Parkinson's disease are important contributors to caregiver distress. Int J Geriatr Psychiatry 14: 866–874

Aarsland D, Larsen JP, Tandberg E, Laake K (2000) Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc 48: 938–942

Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sorensen P (2001) Risk of dementia in Parkinson's disease: a community-based, prospective study. Neurology 56: 730–736

Aarsland D, Laake K, Larsen JP, Janvin C (2002) Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. J Neurol Neurosurg Psychiatry 72: 708–712

Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P (2003a) Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 60: 387–392

Aarsland D, Hutchinson M, Larsen JP (2003b) Cognitive, psychiatric and motor response to galantamine in Parkinson's disease with dementia. Int J Geriatr Psychiatry 18: 937–941

Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP (2003c) Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry 74: 1215–1220

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 9: 357–381

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders. American Psychiatric Association, Washington DC

Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW (2002) Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response. Arch Neurol 59: 102–112

Ballard C, Piggott M, Johnson M, Cairns N, Perry R, McKeith I, Jaros E, O'Brien J, Holmes C, Perry E (2000) Delusions associated with elevated muscarinic binding in dementia with Lewy bodies. Ann Neurol 48: 868–876

Ballard CG, Aarsland D, McKeith I, O'Brien J, Gray A, Cormack F, Burn D, Cassidy T, Starfeldt R, Larsen JP, Brown R, Tovee M (2002) Fluctuations in attention: PD dementia vs DLB with parkinsonism. Neurology 59: 1714–1720

Bedard MA, Pillon B, Dubois B, Duchesne N, Masson H, Agid Y (1999) Acute and long-term administration of anticholinergics in Parkinson's disease: specific effects on the subcortico-frontal syndrome. Brain Cogn 40: 289–313

Bergman J, Lerner V (2002) Successful use of donepezil for the treatment of psychotic symptoms in patients with Parkinson's disease. Clin Neuropharmacol 25: 107–110

Boller F, Passafiume D, Keefe NC, Rogers K, Morrow L, Kim Y (1984) Visuospatial impairment in Parkinson's disease. Role of perceptual and motor factors. Arch Neurol 41: 485–490

Bondi MW, Kaszniak AW, Bayles KA, Vance KT (1993) Contribution of frontal system dysfunction to memory and perceptual abilities in Parkinson's disease. Neuropsychology 7: 89–102

Bosboom JLW, Wolters EC (2004) Psychotic symptoms in Parkinson's disease: pathophysiology and management. Exp Opinion Drug Saf 3: 209–220

Bowen FP, Hoehn MM, Yahr MD (1972) Parkinsonism: alterations in spatial orientation as determined by a route-walking test. Neuropsychologia 10: 355–361

Bowen FP, Kamienny RS, Burns MM, Yahr M (1975) Parkinsonism: effects of levodopa treatment on concept formation. Neurology 25: 701–704

Bradley VA, Welch JL, Dick DJ (1989) Visuospatial working memory in Parkinson's disease. J Neurol Neurosurg Psychiatry 52: 1228–1235

Brown RG, Marsden CD (1986) Visuospatial function in Parkinson's disease. Brain 109 (Pt 5): 987–1002

Bullock R, Cameron A (2002) Rivastigmine for the treatment of dementia and visual hallucinations associated with Parkinson's disease: a case series. Curr Med Res Opin 18: 258–264

Burn DJ, McKeith IG (2003a) Current treatment of dementia with Lewy bodies and dementia associated with Parkinson's disease. Mov Disord 18 [Suppl 6]: S72–S79

Burn DJ, Rowan EN, Minett T, Sanders J, Myint P, Richardson J, Thomas A, Newby J, Reid J, O'Brien JT, McKeith IG (2003b) Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: a cross-sectional comparative study. Mov Disord 18: 884–889

Buytenhuijs EL, Berger HJ, van Spaendonck KP, Horstink MW, Borm GF, Cools AR (1994) Memory and learning strategies in patients with Parkinson's disease. Neuropsychologia 32: 335–342

Cash R, Dennis T, L'Heureux R, Raisman R, Javoy-Agid F, Scatton B (1987) Parkinson's disease and dementia: norepinephrine and dopamine in locus ceruleus. Neurology 37: 42–46

Chan-Palay V, Asan E (1989) Alterations in catecholamine neurons of the locus coeruleus in senile dementia of the Alzheimer type and in Parkinson's disease with and without dementia and depression. J Comp Neurol 287: 373–392

Connor DJ, Salmon DP, Sandy TJ, Galasko D, Hansen LA, Thal LJ (1998) Cognitive profiles of autopsy-confirmed Lewy body variant vs pure Alzheimer disease. Arch Neurol 55: 994–1000

Cooper JA, Sagar HJ (1993) Encoding deficits in untreated Parkinson's disease. Cortex 29: 251–265

Cooper JA, Sagar HJ, Doherty SM, Jordan N, Tidswell P, Sullivan EV (1992) Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. Brain 115 (Pt 6): 1701–1725

Cooper JA, Sagar HJ, Tidswell P, Jordan N (1994) Slowed central processing in simple and go/no-go reaction time tasks in Parkinson's disease. Brain 117 (Pt 3): 517–529

Cummings JL (1993) Frontal-subcortical circuits and human behavior. Arch Neurol 50: 873–880

Cummings JL, Cyrus PA, Bieber F, Mas J, Orazem J, Gulanski B (1998) Metrifonate treatment of the cognitive deficits of Alzheimer's disease. Metrifonate Study Group. Neurology 50: 1214–1221

Davies P, Maloney AJ (1976) Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet 2: 1403

de Smet Y, Ruberg M, Serdaru M, Dubois B, Lhermitte F, Agid Y (1982) Confusion, dementia and anticholinergics in Parkinson's disease. J Neurol Neurosurg Psychiatry 45: 1161–1164

de Vos RA, Jansen EN, Stam FC, Ravid R, Swaab DF (1995) 'Lewy body disease': clinicopathological correlations in 18 consecutive cases of Parkinson's disease with and without dementia. Clin Neurol Neurosurg 97: 13–22

Dubois B, Pillon B (1997) Cognitive deficits in Parkinson's disease. J Neurol 244: 2–8

Elizan TS, Sroka H, Maker H, Smith H, Yahr MD (1986) Dementia in idiopathic Parkinson's disease. Variables associated with its occurrence in 203 patients. J Neural Transm 65: 285–302

Fabbrini G, Barbanti P, Aurilia C, Pauletti C, Lenzi GL, Meco G (2002) Donepezil in the treatment of hallucinations and delusions in Parkinson's disease. Neurol Sci 23: 41–43

Fenelon G, Mahieux F, Huon R, Ziegler M (2000) Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 123 (Pt 4): 733–745

Francis PT, Palmer AM, Snape M, Wilcock GK (1999) The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry 66: 137–147

Gabelli C (2003) Rivastigmine: an update on therapeutic efficacy in Alzheimer's disease and other conditions. Curr Med Res Opin 19: 69–82

Giladi N, Shabtai H, Gurevich T, Benbunan B, Anca M, Korczyn AD (2003) Rivastigmine (Exelon) for dementia in patients with Parkinson's disease. Acta Neurol Scand 108: 368–373

Girotti F, Soliveri P, Carella F, Piccolo I, Caffarra P, Musicco M, Caraceni T (1988) Dementia and cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry 51: 1498–1502

Goldman-Rakic PS (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Plum F, Mountcastle U (eds) Handbook of physiology. The American Physiological Society, Washington, pp 373–417

Gotham AM, Brown RG, Marsden CD (1988) 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain 111 (Pt 2): 299–321

Grace J, Daniel S, Stevens T, Shankar KK, Walker Z, Byrne EJ, Butler S, Wilkinson D, Woolford J, Waite J, McKeith IG (2001) Long-Term use of rivastigmine in patients with dementia with Lewy bodies: an open-label trial. Int Psychogeriatr 13: 199–205

Harding AJ, Halliday GM (2001) Cortical Lewy body pathology in the diagnosis of dementia. Acta Neuropathol (Berl) 102: 355–363

Hovestadt A, De Jong GJ, Meerwaldt JD (1987) Spatial disorientation as an early symptom of Parkinson's disease. Neurology 37: 485–487

Huber SJ, Shuttleworth EC, Freidenberg DL (1989) Neuropsychological differences between the dementias of Alzheimer's and Parkinson's diseases. Arch Neurol 46: 1287–1291

Hughes TA, Ross HF, Musa S, Bhattacherjee S, Nathan RN, Mindham RH, Spokes EG (2000) A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. Neurology 54: 1596–1602

Hurtig HI, Trojanowski JQ, Galvin J, Ewbank D, Schmidt ML, Lee VM, Clark CM, Glosser G, Stern MB, Gollomp SM, Arnold SE (2000) Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology 54: 1916–1921

Hutchinson M, Fazzini E (1996) Cholinesterase inhibition in Parkinson's disease. J Neurol Neurosurg Psychiatry 61: 324–325

Jacobs DM, Marder K, Cote LJ, Sano M, Stern Y, Mayeux R (1995) Neuropsychological characteristics of preclinical dementia in Parkinson's disease. Neurology 45: 1691–1696

Jellinger KA (1999) Neuropathological correlates of mental dysfunction in Parkinson's disease: an update. In: Wolters ECh, Scheltens Ph, Berendse HW (eds) Mental dysfunctions in Parkinson's disease II. APP, Utrecht, pp 82–105

Jellinger KA, Seppi K, Wenning GK, Poewe W (2002) Impact of coexistent Alzheimer pathology on the natural history of Parkinson's disease. J Neural Transm 109: 329–339

Kuhl DE, Minoshima S, Fessler JA, Frey KA, Foster NL, Ficaro EP, Wieland DM, Koeppe RA (1996) In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. Ann Neurol 40: 399–410

Kulisevsky J (2000a) Role of dopamine in learning and memory: implications for the treatment of cognitive dysfunction in patients with Parkinson's disease. Drugs Aging 16: 365–379

Kulisevsky J, Garcia-Sanchez C, Berthier ML, Barbanoj M, Pascual-Sedano B, Gironell A, Estevez-Gonzalez A (2000b) Chronic effects of dopaminergic replacement on cognitive function in Parkinson's disease: a two-year follow-up study of previously untreated patients. Mov Disord 15: 613–626

Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM (1992) L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology (Berl) 107: 394–404

Lange KW, Paul GM, Naumann M, Gsell W (1995) Dopaminergic effects on cognitive performance in patients with Parkinson's disease. J Neural Transm [Suppl] 46: 423–432

Levy G, Tang MX, Cote LJ, Louis ED, Alfaro B, Mejia H, Stern Y, Marder K (2000) Motor impairment in PD: relationship to incident dementia and age. Neurology 55: 539–544

Levy G, Jacobs DM, Tang MX, Cote LJ, Louis ED, Alfaro B, Mejia H, Stern Y, Marder K (2002) Memory and executive function impairment predict dementia in Parkinson's disease. Mov Disord 17: 1221–1226

Lewis SJG, Dove A, Robbins TW, Barker RA, Owen AM (2004) Striatal contributions to working memory: a functional magnetic resonance imaging study in humans. Eur J Neurosci 19: 755–760

Litvan I, MacIntyre A, Goetz CG, Wenning GK, Jellinger K, Verny M, Bartko JJ, Jankovic J, McKee A, Brandel JP, Chaudhuri KR, Lai EC, D'Olhaberriague L, Pearce RK, Agid Y (1998) Accuracy of the clinical diagnoses of Lewy body disease, Parkinson disease, and dementia with Lewy bodies: a clinicopathologic study. Arch Neurol 55: 969–978

Mahieux F, Fenelon G, Flahault A, Manifacier MJ, Michelet D, Boller F (1998) Neuropsychological prediction of dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 64: 178–183

Marder K, Tang MX, Cote L, Stern Y, Mayeux R (1995) The frequency and associated risk factors for dementia in patients with Parkinson's disease. Arch Neurol 52: 695–701

Mattila PM, Roytta M, Torikka H, Dickson DW, Rinne JO (1998) Cortical Lewy bodies and Alzheimer-type changes in patients with Parkinson's disease. Acta Neuropathol (Berl) 95: 576–582

Mattila PM, Rinne JO, Helenius H, Dickson DW, Roytta M (2000) Alpha-synuclein-immunoreactive cortical Lewy bodies are associated with cognitive impairment in Parkinson's disease. Acta Neuropathol (Berl) 100: 285–290

Mattila PM, Roytta M, Lonnberg P, Marjamaki P, Helenius H, Rinne JO (2001) Choline acetytransferase activity and striatal dopamine receptors in Parkinson's disease in relation to cognitive impairment. Acta Neuropathol (Berl) 102: 160–166

Mayeux R, Stern Y, Sano M, Cote L, Williams JB (1987) Clinical and biochemical correlates of bradyphrenia in Parkinson's disease. Neurology 37: 1130–1134

Mayeux R, Stern Y, Rosenstein R, Marder K, Hauser A, Cote L, Fahn S (1988) An estimate of the prevalence of dementia in idiopathic Parkinson's disease. Arch Neurol 45: 260–262

Mayeux R, Chen J, Mirabello E, Marder K, Bell K, Dooneief G, Cote L, Stern Y (1990) An estimate of the incidence of dementia in idiopathic Parkinson's disease. Neurology 40: 1513–1517

Mayeux R, Denaro J, Hemenegildo N, Marder K, Tang MX, Cote LJ, Stern Y (1992) A population-based investigation of Parkinson's disease with and without dementia. Relationship to age and gender. Arch Neurol 49: 492–497

McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 47: 1113–1124

McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, Cicin-Sain A, Ferrara R, Spiegel R (2000a) Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 356: 2031–2036

McKeith IG (2000b) Spectrum of Parkinson's disease, Parkinson's dementia, and Lewy body dementia. Neurol Clin 18: 865–902

McKeith IG, Grace JB, Walker Z, Byrne EJ, Wilkinson D, Stevens T, Perry EK (2000c) Rivastigmine in the treatment of dementia with Lewy bodies: preliminary findings from an open trial. Int J Geriatr Psychiatry 15: 387–392

Mesulam MM, Mufson EJ, Levey AI, Wainer BH (1983a) Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. J Comp Neurol 214: 170–197

Mesulam MM, Mufson EJ, Wainer BH, Levey AI (1983b) Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1–Ch6). Neuroscience 10: 1185–1201

Oades RD, Halliday GM (1987) Ventral segmental (A10) system: neurobiology. 1. Anatomy and connectivity. Brain Res 434: 117–165

Ogden JA, Growdon JH, Corkin S (1990) Deficits on visuospatial tests involving forward planning in high-functioning Parkinsonians. Neuropsychiatr Neuropsychol Behav Neurol 3: 125–139

Owen AM, Beksinska M, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, Sahakian BJ, Robbins TW (1993) Visuospatial memory deficits at different stages of Parkinson's disease. Neuropsychologia 31: 627–644

Owen AM, Iddon JL, Hodges JR, Summers BA, Robbins TW (1997) Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropsychologia 35: 519–532

Owen AM, Doyon J, Dagher A, Sadikot A, Evans AC (1998) Abnormal basal ganglia outflow in Parkinson's disease identified with PET. Implications for higher cortical functions. Brain 121 (Pt 5): 949–965

Paulus W, Jellinger K (1991) The neuropathologic basis of different clinical subgroups of Parkinson's disease. J Neuropathol Exp Neurol 50: 743–755

Perry EK, Curtis M, Dick DJ, Candy JM, Atack JR, Bloxham CA, Blessed G, Fairbairn A, Tomlinson BE, Perry RH (1985) Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. J Neurol Neurosurg Psychiatry 48: 413–421

Perry EK, McKeith I, Thompson P, Marshall E, Kerwin J, Jabeen S, Edwardson JA, Ince P, Blessed G, Irving D (1991) Topography, extent, and clinical relevance of neurochemical deficits in dementia of Lewy body type, Parkinson's disease, and Alzheimer's disease. Ann NY Acad Sci 640: 197–202

Perry EK, Johnson M, Kerwin JM, Piggott MA, Court JA, Shaw PJ, Ince PG, Brown A, Perry RH (1992) Convergent cholinergic activities in aging and Alzheimer's disease. Neurobiol Aging 13: 393–400

Perry EK, Irving D, Kerwin JM, McKeith IG, Thompson P, Collerton D, Fairbairn AF, Ince PG, Morris CM, Cheng AV (1993) Cholinergic transmitter and neurotrophic activities in Lewy body dementia: similarity to Parkinson's and distinction from Alzheimer disease. Alzheimer Dis Assoc Disord 7: 69–79

Pillon B, Dubois B, Cusimano G, Bonnet AM, Lhermitte F, Agid Y (1989) Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? J Neurol Neurosurg Psychiatry 52: 201–206

Pillon B, Deweer B, Agid Y, Dubois B (1993) Explicit memory in Alzheimer's, Huntington's, and Parkinson's diseases. Arch Neurol 50: 374–379

Pillon B, Deweer B, Vidailhet M, Bonnet AM, Hahn-Barma V, Dubois B (1998) Is impaired memory for spatial location in Parkinson's disease domain specific or dependent on 'strategic' processes? Neuropsychologia 36: 1–9

Pillon B, Boller F, Levy R, Dubois B (2001) Cognitive deficits and dementia in Parkinson's disease. In: Boller F, Cappa S (eds) Aging and dementia, vol 6. Elsevier Science B.V., Amsterdam, pp 311–371

Poewe W (2003) Psychosis in Parkinson's disease. Mov Disord 18 [Suppl 6]: S80–S87

Ransmayr G, Schmidhuber-Eiler B, Karamat E, Engler-Plorer S, Poewe W, Leidlmair K (1987) Visuoperception and visuospatial and visuorotational performance in Parkinson's disease. J Neurol 235: 99–101

Raskin SA, Borod JC, Tweedy JR (1992) Set-shifting and spatial orientation in patients with Parkinson's disease. J Clin Exp Neuropsychol 14: 801–821

Read NL, Hughes TA, Dunn EM, Nirodi P, Branton T, Mindham RH, Spokes EG (2001) Dementia in Parkinson's disease: incidence and associated factors at 14-years of follow-up. Parkinsonism and Related Disorders 7: S109

Reading PJ, Luce AK, McKeith IG (2001) Rivastigmine in the treatment of parkinsonian psychosis and cognitive impairment: preliminary findings from an open trial. Mov Disord 16: 1171–1174

Richard IH, Papka M, Rubio A, Kurlan R (2002) Parkinson's disease and dementia with Lewy bodies: one disease or two? Mov Disord 17: 1161–1165

Rinne JO, Rummukainen J, Paljarvi L, Rinne UK (1989) Dementia in Parkinson's disease is related to neuronal loss in the medial substantia nigra. Ann Neurol 26: 47–50

Rogers RD, Sahakian BJ, Hodges JR, Polkey CE, Kennard C, Robbins TW (1998a) Dissociating executive mechanisms of task control following frontal lobe damage and Parkinson's disease. Brain 121 (Pt 5): 815–842

Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT (1998b) A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 50: 136–145

Rowe J, Stephan KE, Friston K, Frackowiak R, Lees A, Passingham R (2002) Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. Brain 125: 276–289

Samochocki M, Zerlin M, Jostock R, Groot Kormelink PJ, Luyten WH, Albuquerque EX, Maelicke A (2000) Galantamine is an allosterically potentiating ligand of the human alpha4/beta2 nAChR. Acta Neurol Scand [Suppl] 176: 68–73

SantaCruz K, Pahwa R, Lyons K, Troster A, Handler M, Koller W, DeCarli C (1999) Lewy body, neurofibrillary tangle and senile plaque pathology in Parkinson's disease patients with and without dementia. Neurology 52: A476–A477

Scatton B, Javoy-Agid F, Rouquier L, Dubois B, Agid Y (1983) Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res 275: 321–328

Scheltens Ph (1999) Dementia in Parkinon's disease: subclinical Alzheimer's disease? In: Wolters ECh, Scheltens Ph, Berendse HW (eds) Mental dysfunctions in Parkinson's disease II. APP, Utrecht, pp 189–193

Smith EE, Jonides J (1999) Storage and executive processes in the frontal lobes. Science 283: 1657–1661

Smith MC, Goldman WP, Janer KW, Baty JD, Morris JC (1998) Cognitive speed in nondemented Parkinson's disease. J Int Neuropsychol Soc 4: 584–592

Stern Y, Marder K, Tang MX, Mayeux R (1993) Antecedent clinical features associated with dementia in Parkinson's disease. Neurology 43: 1690–1692

Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C (2000) A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 54: 2269–2276

Taylor AE, Saint-Cyr JA, Lang AE (1986) Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. Brain 109: 845–883

Taylor AE, Saint-Cyr JA, Lang AE (1990) Memory and learning in early Parkinson's disease: evidence for a ''frontal lobe syndrome''. Brain Cogn 13: 211–232

Thierry AM, Tassin JP, Blanc G, Glowinski J (1978) Studies on mesocortical dopamine systems. Adv Biochem Psychopharmacol 19: 205–216

Tiraboschi P, Hansen LA, Alford M, Sabbagh MN, Schoos B, Masliah E, Thal LJ, Corey-Bloom J (2000) Cholinergic dysfunction in diseases with Lewy bodies. Neurology 54: 407–411

Werber EA, Rabey JM (2001) The beneficial effect of cholinesterase inhibitors on patients suffering from Parkinson's disease and dementia. J Neural Transm 108: 1319–1325

Whitehouse PJ, Hedreen JC, White CL, III, Price DL (1983) Basal forebrain neurons in the dementia of Parkinson disease. Ann Neurol 13: 243–248

Wilson RS, Kaszniak AW, Klawans HL, Garron DC (1980) High speed memory scanning in parkinsonism. Cortex 16: 67–72

Wolters EC (2001) Psychiatric complications in the treatment of Parkinson's disease. Adv Neurol 86: 385–393

Wolters EC, Francot CMJE (1998) Mental dysfunctions in Parkinson's disease. Parkinsonism Rel Disord 4: 107–112

Woods SP, Troster AI (2003) Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease. J Int Neuropsychol Soc 9: 17–24

Authors' address: E.Ch. Wolters, Department of Neurology, Vrije Universiteit, University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands, e-mail: e.wolters@vumc.nl