Movement disorders *Review*

Biomarkers for Dementia and Mild Cognitive Impairment in Parkinson's Disease

Manuel Delgado-Alvarado[1,2], Belén Gago[1,2*], Irene Navalpotro-Gomez[1,2], Haritz Jiménez-Urbieta[1,2], María C. Rodriguez-Oroz[1,2,3,4,5,6]

[1]Biodonostia Health Research Institute, San Sebastián, Spain.

[2]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain.

[3]Neurology Department, University Hospital Donostia, San Sebastián, Spain.

[4]Ikerbasque (Basque Foundation for Science), Bilbao, Spain.

[5] Basque Center on Cognition, Brain and Language (BCBL), San Sebastián, Spain.

[6] Physiology Department, Medical School University of Navarra, Pamplona, Spain.

*Current address: Universidad de Málaga, Instituto de Investigación Biomédica, Facultad de Medicina, Málaga, Spain.

Corresponding author:

Maria C Rodriguez-Oroz Tel.: +34943006258. Fax: +34943005250;

E-mail address: maria.rodriguezoroz@biodonostia.org

Article content: 62 pages; 5287 words; 298 references; 3 tables; 2 images; 2 supplementary tables

Running Title: Biomarkers and cognition in Parkinson's disease

Keywords: Parkinson's disease; mild cognitive impairment; biomarkers; dementia.

Financial Disclosure/Conflict of Interest: the authors have no conflict of interests to declare

Funding Sources: Institute of Health Carlos III (ISCIII), grants PI08/1539 and PI14/00763; Government of the Basque Country, grants 2011111074 and SAIO12-PE12BN012; and CIBERNED. M.D.-A. is funded by a Basque Country Ph.D. Studentship and Jesús de Gangoiti Barrera Foundation grant

Abstract

Cognitive decline is one of the most frequent and disabling non-motor features of Parkinson´s disease. Around 30% of patients with Parkinson's disease experience mild cognitive impairment, a well-established risk factor for the development of dementia. However, mild cognitive impairment in patients with Parkinson's disease is a heterogeneous entity that involves different types and extents of cognitive deficits. Since it is not currently known which type of mild cognitive impairment confers a higher risk of progression to dementia, it would be useful to define biomarkers that could identify these patients to better study disease progression and possible interventions. In this sense, the identification among patients with Parkinson's disease and mild cognitive impairment of biomarkers associated with dementia would allow the early detection of this process. This review summarizes studies from the last 25 years that have assessed potential biomarkers of dementia and mild cognitive impairment in Parkinson's disease patients. Despite the potential importance, no biomarker has as yet been validated. However, features such as low levels of epidermal and insulin-like growth factors or uric acid in plasma/serum and of Aß in CSF, reduction of cerebral cholinergic innervation and metabolism measured by

PET mainly in posterior areas, and hippocampal atrophy in MRI might be indicative of dementia or of subgroups of patients with distinct subtypes of cognitive deficits with a distinct risk of dementia. Therefore, longitudinal studies combining the existing techniques and new approaches will be needed to identify patients at higher risk of dementia.

INTRODUCTION

It is only in recent decades that cognitive impairment has become recognized as a relevant clinical manifestation of PD, the prevalence of dementia reaching 80% in long-term patients.[1, 2] Mild cognitive impairment (MCI) is also highly prevalent in PD (PD-MCI: mean 26.7%; range 18.9%–38.2%)[3] and it is known to be a risk factor for dementia (PDD).[3-7] PD-MCI is defined as cognitive decline that is not normal for the age and educational level of the patient but that is not associated with impaired functional activity.[8] However, PD-MCI is a heterogeneous entity that covers several forms of cognitive impairment in function of the number and type of cognitive domains affected.[8] It is not currently known which types of PD-MCI confer a higher risk of progression to dementia. In this sense, useful biomarkers are needed that can predict future outcome or that are useful to longitudinally track the underlying disease pathology in an objective way. Thus, there is increasing interest in the search for biomarkers that could aid in the identification of such PD-MCI patients. The assessment of biomarkers already associated with PDD in PD-MCI patients is one interesting approach to define subtypes of MCI that share biological features with dementia. In this review, we summarize the data currently available regarding the biological markers of dementia and MCI in PD.

LITERATURE SEARCHING STRATEGY

The literature in Medline (PubMed) from 1990 to July 2015 was reviewed using the free search terms Parkinson's disease AND (dementia OR mild cognitive impairment), combined with the following terms/sets of terms: cerebrospinal fluid; blood OR plasma; genes OR DNA OR polymorphism; magnetic resonance imaging; PET; SPECT; electroencephalogram; magnetoencephalography; evoked potentials. The search was limited to articles in English and the reference lists were searched for additional publications. Since the concept of PD-MCI was introduced only a few years ago and the diagnostic criteria (MDS Task Force)[8] were only recently adopted, some studies only distinguished between PDD and non-demented PD patients (PDND), while in others cognitively normal PD patients (PDCN) and PD-MCI were considered. Notably, several studies did not specify whether PD patients were PDCN or PDND, referring to them just as PD. In this review we will maintain the nomenclature used in the original papers. In addition to the studies in which a diagnosis of PDD or PD-MCI was indicated, those studying correlations between biomarkers and cognitive performance have been considered. Studies in which cognitive diagnosis was only based on subjective medical assessment, without any formal neuropsychological evaluation, case reports and case series were excluded.

CEREBROSPINAL FLUID

The presence of Lewy bodies (LB), amyloid plaques and neurofibrillary tangles in the neocortex and limbic system is associated with dementia[9-13] and MCI[14, 15] in PD. Hence, the levels of amyloid-ß (Aß), tau protein and α-synuclein have been studied in the

cerebrospinal fluid (CSF) of PD patients (Table 1). In most studies, there was less Aß in PDD than in healthy controls[16-20] and PDND[16, 18, 19] patients, and lower levels of Aß were associated with progression to dementia in PDND patients[21] and a deterioration in attention,[22] executive function,[22, 23] memory[22, 23] and global cognition.[24] By contrast, the data for total (t-tau) and phosphorylated tau (p-tau) are less consistent, with increased[16, 18, 25, 26] or unchanged levels[17, 27-30] in PDD patients. In PD-MCI patients, there was less[17] or similar[31, 32] Aß to that in PDCN patients, while t-tau was higher[32] or no different,[17, 31] and p-tau was comparable in both.[17, 31, 32] Interestingly, in PDND patients, low levels of Aß[24, 25, 33-35] and a low Aß 1-42/total tau[24, 34] ratio were associated with impairment in several cognitive domains or tests: attention and working memory,[34] executive function,[35] memory,[33, 35] and phonemic[21] and semantic fluency.[34] Although the total α-synuclein was similar in PDD and PDND patients or controls in initial studies,[26, 36] technically more advanced analyses show that PDD patients have more oligomeric forms of α-synuclein,[18, 37] and a higher total α-synuclein concentration was associated with a faster decline in cognitive performance in *de novo* patients.[38] However, most studies fail to find any association between total or oligomeric α-synuclein and cognition in PDND patients.[24, 35, 39]

Table 1. Summary of the studies that evaluated CSF amyloid ß1-42 (Aß1-42), total tau (t-tau), phosphorylated tau (p-tau), total α-synuclein (t-α-syn), and oligomeric α-synuclein (o-α-syn) as potential biomarkers for PDD or PD-MCI.

	STUDIED BIOMARKERS					PATIENTS					COGNITIVE EVALUATION / DIAGNOSTIC CRITERIA	MAIN RESULTS/FINDINGS
	Aß1-42	**T-tau**	**P-tau**	**T-α-syn**	**O-α-syn**	**PDND**	**PDCN**	**PDD**	**PD-MCI**	**Control**		
PDD												
Jansen et al., 1998[27]		+	+			67		48		41	MMSE / PDD if< 26	
Parnetti et al., 2008[28]	+	+	+			20		8		20	MMSE / PDD by McKeith et al., 1996	
Maetzler et al., 2011[41]	+	+				21		10		39	MMSE / PDD by DSM-IV	No differences
Maetzler et al., 2012[30]	+	+				77		26		72	MMSE / PDD by DSM-IV and MDS Task Force	
Wennström et al., 2013[36]				+		38		22		52	MMSE / PDD by MDS Task Force	
Mollenhauer et al., 2006[16]	+	+				23		73		41	MMSE / PDD if< 25	PDD vs. PDND and C: ↓ Aß1-42 PDD vs. C: ↑ t-tau
Maetzler et al., 2009[20]	+					14		12			MMSE / PDD by DSM-IV	PDD vs. PDND: ↓ Aß42
Compta et al., 2009[25]	+	+				20		20		30	MMSE, attention and working memory, executive, memory, language, visuospatial / PDD by DSM-IV-R and MDS Task Force	PDD vs. PDND and C: ↑ t-tau PDND: ↓ Aß1-42 positively correlated with phonemic fluency
Compta et al., 2011[19]	+	+	+			19		19		9	MMSE / PDD by DSM-IV-R and MDS Task Force	PDD vs. PDND and C: ↓ Aß1-42 ↑ t-tau and p-tau in a subgroup of PDND and PDD with the rs242557 A-allele of *MAPT* and with levels of Aß1-42 < 500 pg/mL

Hall et al., 2012[26]	+	+	+	+		90		33		107	MMSE / PDD by MDS Task Force	PDD vs. PDND: ↑ p-tau No differences in Aß1-42 or t-α-syn
Vranová et al., 2014[29]	+	+				27		14		24	MMSE, attention and working memory, executive, memory / PDD by MDS Task Force	PDD vs. PDND: ↑ t-tau/Aß1-42 index No differences in Aß1-42 or t-tau
Hansson et al., 2014[37]				+	+	30				98	MMSE / PDD by MDS Task Force	PDD vs. C: ↑ o-α-syn
Compta et al., 2015[18]	+	+		+	+	21		20		13	MMSE / PDD by MDS Task Force	PDD vs. PDND and C: ↓ Aß1-42 and ↑ t-tau PDD vs. C: ↑ o-α-syn
PD-MCI												
Beyer et al., 2013[31]	+ Aß38, Aß40	+	+				73		18		MMSE, attention and working memory, executive, memory, visuospatial / PD-MCI if performance < 1.5 SDs below predicted level in ≥ 1 cognitive domains	No differences
Montine et al., 2010[17]	+	+	+				41	11	58	150	CDR / PDD by MDS Task Force; PD-MCI by CDR=0.5	PDD vs. C: ↓ Aß1-42 PD-MCI vs. C: ↓ Aß1-42 No differences in t-tau and p-tau
Yu et al., 2014[32]	+	+	+				26		36	31	MMSE, MOCA / PDD and PD-MCI by MDS Task Force	PD-MCI vs. PDCN and C: ↑ t-tau PD-MCI: MOCA negatively correlated with t-tau
PDND*												
Alves et al., 2010[33]	+ Aß38, Aß40	+	+			109				36	MMSE, attention and working memory, executive, memory, visuospatial / PDD by MDS Task Force	Positive correlation between Aß42, Aß38 and Aß40 and memory
Siderowf et al., 2010[22 §]	+	+	+			45					DRS-2, memory, attention and working memory, initiation-perseveration, construction, and conceptualization / PDD if DRS-2 < 124	↓ Aß1-42 associated with decline in attention, conceptualization, memory and initiation/perseveration

Leverenz et al., 2011[34]	+	+				22		MMSE, attention and working memory, memory, semantic fluency, executive, processing speed / PDD by consensus panel based on CDR	Positive correlation between Aß1-42, attention and working memory Positive correlation between Aß42/t-tau and working memory, attention and semantic fluency
Compta et al., 2013[21 §]	+					27		MMSE, executive, memory, language, visuospatial / PDD by MDS Task Force	↓ Aß1-42 in dementia-converters Positive correlation between Aß1-42 and lower phonemic fluency
Stewart et al., 2014[38 §]				+		304		MMSE, attention and working memory, memory, visuospatial / PDD if MMSE < 23	↑ t-α-syn at baseline predicts faster cognitive decline
Parnetti et al., 2014[24 §]	+	+	+	+	+	44	25	MMSE, MOCA	Aß1-42 negative correlation with decline in MMSE and MOCA Aß1-42 and t-tau negative correlation with decline in MMSE
Liu et al., 2015[23 §]	+	+	+			403		MMSE, attention and working memory, executive, memory, visuospatial	No association with cognitive function at baseline T-tau and p-tau/Aß1-42 predicted decline in memory and executive function
Buddhala et al., 2015[39]	+	+	+	+		77	30	CRD, Attention and working memory, executive, memory, language, visuospatial / PDD by CRD	No association with cognition
Stav et al., 2015[35]	+	+	+	+		31	34	Attention and working memory, executive, visuospatial	Positive correlation between Aß1-42 and memory and response inhibition
Backstrom et al., 2015[47 §]	+	+	+	+		99		Attention and working memory, executive, memory, visuospatial / PDD and PD-MCI by modified MDS Task Force	↓ Aß1-42 associated with progression to PDD

Abbreviations. ***Subjects:*** PDND, Parkinson's disease non-demented; PDD, Parkinson's disease with dementia; PD-MCI, Parkinson's disease with mild cognitive impairment; PDCN, Parkinson's disease cognitively normal; C, control. ***Cognitive assessment:*** MMSE, Mini Mental State Examination; MOCA, Montreal Cognitive

Assessment; DRS-2, Mattis Dementia Rating Scale (version 2); MDS, Movement Disorders Society; CDR, Clinical Dementia Rating; DSM, Diagnostic and Statistical Manual of Mental Disorders.

* In these studies PDD patients were excluded according to the criteria shown. No distinction between PDCN and PD-MCI was considered in PDND patients
§ Longitudinal studies

Proteins involved in inflammatory processes, oxidative stress and neuronal viability have also been investigated (Supplementary table 1). More C-reactive protein (CRP) was found in PDD patients than in PDND and controls,[40] and interleukin-6 (IL-6) and IL-1β were more elevated in PD-MCI than in PDCN patients or controls.[32] PD-MCI patients also had less interferon-γ (IFN-γ) and tumor necrosis factor α (TNF-α), and higher levels of nitric oxide and hydroxyl radical than controls.[32] In addition, some of these proteins were associated with global cognition in PDND[40] and PD-MCI patients.[32] Uric acid (UA),[41] a scavenger of free radicals, and cystatin C,[42] which has anti-amyloidogenic properties, were also reduced in PDD and dementia with Lewy bodies (DLB) patients. Other proteins, such as brain derived neurotrophic factor (BDNF), eotaxin, ferritin, hypocretin and transthyretin[32, 34, 40, 43, 44] did not differ between PDD and PDND or controls. Finally, recent proteomic analyses reveal that some proteins involved in signaling pathways, axonal guiding or protein folding[45, 46] were differentially expressed in PDD and PDND patients. Interestingly, a profile characterized by low Aß1-42, high neurofilament light chain protein and high heart fatty acid-binding protein was associated with progression to PDD, with a relatively high diagnostic accuracy.[47]

Despite some variability, reduced Aß in PDD patients and in PDND who progressed to dementia appears to be relatively consistent.[16-24] Along with the heterogeneity in Aß concentrations in PD-MCI[17, 31, 32] and the fact that low Aß correlates with specific cognitive deficits in PDND patients,[24, 25, 33-35] this suggests that Aß protein might represent a useful biomarker to identify specific types of PD-MCI that might be at higher risk of suffering dementia (patients with concomitant Alzheimer's disease [AD] or AD pathological changes). Although based on few studies, an increase in α-synuclein oligomers should also be considered.[18, 26, 36-38] Differences in proteins related to

inflammation,[32, 40] oxidative stress[41] and cell survival are also promising.[45, 46] Proteomic analysis might also be considered to validate and expand current data in future studies.

Supplementary table 1. Summary of studies assessing CSF potential biomarkers for PDD and PD-MCI other than neuropathologic proteins and studies assessing potential biomarkers in plasma/serum and urine.

	BIOMARKER	PATHWAY / MECHANISM	PATIENTS	COGNITIVE EVALUATION / DIAGNOSTIC CRITERIA	MAIN FINDINGS / RESULTS
CSF					
PDD					
Kuiper et al., 1994[43]	Ferritin	Iron carrier	PDND (n=72) PDD (n=15) C (n=20)	PDD by DSM-III-R	No differences
Compta et al., 2009[44]	Hypocretin	Neuropeptid	PDND (n=21) PDD (n=20) C (n=22)	MMSE / PDD by DSM-IV-R and MDS Task Force	No differences
Maetzler et al., 2010[42]	Cystatin C	Antiamyloidogenic	PDND (n=52) PDD (n=24) C (n=36)	MMSE / PDD by DSM-IV	PDD vs. C: ↓
Maetzler et al., 2011[41]	Uric acid	Oxidative stress	PDND (n=55) PDD (n=20) C (n=76)	MMSE / PDD by DSM-IV	PDD/DLB vs. PDND: ↓
Maetzler et al., 2012[30]	Transthyretin	Thyroxine and retinol carrier	PDND (n=77) PDD (n=26) C (n=72)	MMSE / PDD by DSM-IV and MDS Task Force	No differences
Jesse et al., 2012[45]	Serpin A1	Serine protease inhibitor	PDND (n=24) PDD (n=21) C (n=24)	MMSE, attention and working memory, executive, memory, language, visuospatial / PDD by DSM-IV	Differentially sialylated isoforms of Serpin A1 identified PDD vs. PDND with 100 % sensitivity and 58 % specificity
Lehnert et al., 2012[46]	Eotaxin, Netrin G1, non-receptor Tyrosine-kinase type 13	Miscellaneous	PD (n=12) PDD (n=12) C (n=12)	MMSE, executive, visuospatial / PDD by DSM-IV	PDD vs. C: ↑ Netrin G1 and non-receptor Tyrosine-kinase type 13
Hall et al., 2012[26]	Neurofilament light chain	Neuronal structure	PDND (n=90) PDD (n =33) C (n=107)	MMSE / PDD by MDS Task Force	PDD vs. PDND: ↑

Lindqvist et al., 2013[40]	CRP, IL-6, TNF- α, IP10, MIP1β, MCP1	Inflammation/immune response	PDND (n=71) PDD (n=16) C (n=33)	MMSE / PDD by MDS Task Force	PDD vs. PDND and C: ↑ CRP PDND: IL-6 negative correlation with MMSE.
Wennström et al., 2013[36]	Neurosin	Serin protease	PDND (n=38) PDD (n=22) C (n=52)	MMSE / PDD by MDS Task Force	No differences
PD-MCI					
Yu et al., 2014[32]	IL-1β, IL-6, TNF- α, INF-γ, PGE_2 OH, H_2O_2, NO	Inflammation/immune response Oxidative stress	PDCN (n=26) PD-MCI (n=36) C (n=31)	MMSE, MOCA / PD-MCI by MDS Task Force	PD-MCI vs. C: ↑ IL-1β and IL-6, ↓TNF-α and INF-γ. ↑ OH and NO. No differences in H_2O_2 PD-MCI vs. PDCN: ↑ IL-6. No differences in PGE2 PD-MCI: IL-6 negative correlation with MOCA.
PDND					
Leverenz et al., 2011[34]	Brain Derived Neurotrophic Factor	Neurotrophic factors	PDND (n=22)	MMSE, attention and working memory, memory, semantic fluency, executive, processing speed / PDD by consensus panel based on CDR	Positive correlation with attention and working memory
Backstrom et al., 2015[47]	Neurofilament light chain protein, heart fatty acid-binding protein	Neuronal structure / Lipid metabolism	PDND (n=99) *Longitudinal (9 years)*	Attention and working memory, executive, memory, visuospatial / PDD and PD-MCI by MDS Task Force	↑ neurofilament light chain protein and heart fatty acid-binding protein associated with progression to PDD
PLASMA/SERUM					
PDD / PDND					
Bialecka et al., 2012[48]	Homocysteine (P)	Cardiovascular risk	PDND (n=153) PDD (n=64) C (n=254)	MMSE, attention and working memory, executive, memory, language / PDD by MDS Task Force	PDD vs. PDND: ↑
Song et al., 2013[49]	Homocysteine (P)	Cardiovascular risk	PDND (n=33) PDD (n=28) C (n=48)	MMSE, CDR / PDD by DSM-IVR	PDD vs. PDND: ↑
Chen-Plotkin et al., 2011[64]	Epidermal Growth Factor (P)	Neurotrophic factors	PDND (n=70) *Longitudinal (21 months)*	DRS-2 / PDD if ≤ 5	Positive correlation with cognitive status at baseline and ↓ associated with greater risk of cognitive decline at follow-up

Song et al., 2013[56]	High-sensitivity C-reactive protein (S)	Inflammation/immune response	PDND (n=72) PDD (n=45) C (n=84)	MMSE, CDR / PDD by DSM-IV-R	No differences
Peterson et al., 2013[54]	Vitamin D (P)	Neurotrophic factors	PDND (n=225) PDD (n=61)	MMSE, MOCA, DRS, attention and working memory, executive, memory, visuospatial / PDD by DSM-IV	No differences. PDND+PDD: positive correlation with memory and semantic fluency
González-Aramburu et al., 2014[55]	Uric acid (S)	Oxidative stress	PDND (n=271) PDD (n=72)	MMSE, attention and working memory, executive, memory, visuospatial / PDD by MDS Task Force	No differences
PD-MCI/ PDCN/PDD					
Mielke et al., 2013[73]	Ceramide and monohexosylceramide (P)	Lipid metabolism	PDCN (n=26) PD-MCI (n=14) PDD (n=12) C (n=5)	MMSE, attention and working memory, executive / PD-MCI and PDD by MDS Task Force	PDD+PD-MCI vs. PDCN: ↑ ceramide C16:0, C18:0, C20:0, C22:0, and C24:0 and monohexosylceramide C16:0, C20:0, and C24:0 species
Rodriguez-Oroz et al., 2014[51]	Homocysteine (P)	Cardiovascular risk	PDCN (n=37) PD-MCI (n=22) PDD (n=30) C (n=30)	MMSE, attention and working memory, executive, memory, language / MCI by Petersen et al., 1999; PDD by DSM-IV	No differences
Li et al., 2015[70]	Phospholipids (P)	Lipid metabolism	PDCN (n=44) PD-MCI (n=41) C (n=75)	MOCA / PD-MCI if < 26	PD-MCI vs. PDND and C: ↑
PDND or PD					
O'Suilleabhain et al., 2004[50]	Homocysteine (P)	Cardiovascular risk	PDND (n=97)	MMSE, attention and working memory, executive, memory, language, visuospatial	↑ associated with worse performance in visuospatial and executive functions
Hassin-Baer et al., 2006[52]	Homocysteine (P)	Cardiovascular risk	PD (n=72)	MMSE, FAB, attention and working memory, executive, memory, language, visuospatial	No association with cognitive performance
Camicioli et al.,	Homocysteine (P)	Cardiovascular risk	PDND (n=51)	MMSE, DRS, executive, visuospatial	No association with cognitive performance

2009[53]			C (n=50)		
Annanmaki et al. 2008[57]*	Uric acid (P)	Oxidative stress	PD (n=40)	MMSE, attention and working memory, executive, memory, language, visuospatial	Positive correlation with lower performance in several cognitive tests
Moccia et al., 2014[58]	Uric acid (S)	Oxidative stress	PD (n=80)	MMSE, attention and working memory, memory	↓ associated with impairment of attention/memory
Moccia et al., 2014[59]	Uric acid (S)	Oxidative stress	PD (n=69) *Longitudinal (2 years)*	MMSE, attention and working memory, memory	↓ associated with worsening in attention/memory
Connolly et al., 2008[72]**	8,12-isoprostane$F_{2\alpha}$-VI (P)	Lipid metabolism	PD (n=36) C (n=30)	MMSE, executive, memory	No association with cognitive performance
Sclazo et al., 2010[61]	IL-6 (S)	Inflammation/immune response	PDND (n=44)	MMSE	Negative correlation with MMSE
Menza et al., 2010[60]	IL-6, TNF- α (P)	Inflammation/immune response	PDND (n=52)	MMSE, attention and working memory, executive, memory, language	Both markers: negative correlation with global cognition
Hassin-Baer et al., 2011[52]	CRP (P)	Inflammation/immune response	PD (n=73)	MMSE, FAB, attention and working memory, executive, memory, language, visuospatial	No association with cognitive performance
Pellecchia et al., 2013[63]	Epidermal Growth Factor (S)	Neurotrophic factors	PD (n=65) *Longitudinal (2 years)*	MMSE, attention and working memory, executive, memory, visuospatial	Positive correlation with performance in semantic fluency and color naming task of Stroop at follow up
Pelleccia et al., 2014[65]	Insulin-like growth factor-1 (S)	Neurotrophic factors	PD (n=65) *Longitudinal (2 years)*	MMSE, attention and working memory, executive, memory, visuospatial	↓ associated with faster decline in memory and executive function
Ma et al., 2015[66]	Insulin-like growth factor-1 (P)	Neurotrophic factors	PD (n=100) C (n=76)	MMSE	Positive correlation with MMSE score

Abbreviations. ***Biomarkers:*** (P), plasma; (S), serum; CRP, C reactive protein; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor alpha; IFN-γ, Interferon gamma; PGE_2, Prostaglandin E_2; IP10, Interferon gamma-induced protein-10; MIP1β, Macrophage inflammatory protein-1; MCP1, Monocyte chemotactic protein-1; Hcy, Homocystein**.** ***Subjects:*** PDD, Parkinson's disease with dementia; PD-MCI, Parkinson's disease with mild cognitive impairment; PDND, Parkinson's disease non-demented; PDCN, Parkinson's disease cognitively normal; C, control**.** ***Cognitive assessment****:* MMSE, Mini Mental State Examination; MOCA, Montreal Cognitive Assessment; MDS, Movement Disorders Society; FAB, Frontal Assessment Battery; DSM, Diagnostic and Statistical Manual of Mental Disorders

*Low urine uric acid levels associated with worse performance on information, similarities, BD, picture completion, DS-B, rule shift cards, 10-CRT, statement verification, cognitive processing vigilance.
** Urine levels not associated with cognitive performance

OTHER BIOLOGICAL FLUIDS: PLASMA/SERUM AND URINE

Apart from CSF, other biological fluids represent an attractive source of biomarkers due to the ease of obtaining samples (Supplementary table 1). Regarding plasmatic homocysteine, while some studies associated higher levels with dementia and worse cognitive outcome,[48-50] others failed to find any relationship with PD-MCI, dementia or neuropsychological performance.[51-53]

Plasma or serum levels of proteins involved in inflammation (CRP), oxidative stress (UA) or neuroprotection (vitamin D, transthyretin) were no different in PDD and PDND patients.[30, 54-56] However, in PDND patients, low UA concentrations was associated with a worse outcome in global cognition,[57, 58] attention, and memory;[59] high vitamin D levels with better semantic fluency and memory;[54] and high concentrations of IL-6,[60, 61] TNF-α,[60] and IFN γ-induced protein 10[62] with lower cognitive scores. Importantly, low levels of epidermal growth factor (EGF)[63, 64] and insulin-like growth factor (ILGF)[65] have certain predictive value for the development of dementia and cognitive decline, and ILGF positively correlates with global cognition[66] and executive function.[65] Interestingly, after cognitive rehabilitation plasma BDNF levels increased in PD-MCI patients.[67]

In addition to proteins, lipids have also been evaluated as abnormal lipid peroxidation may play a role in the pathogenesis of PD and other neurodegenerative diseases.[68, 69] Whereas plasma levels of phospholipids were higher in PD-MCI than in PDCN patients,[70] prostaglandin isomers derived from free radical peroxidation of polyunsaturated fatty acids[71] (i.e. F2-isoprostanes) did not differ between PDD and PDND patients, nor were they associated with the severity of cognitive impairment.[72] Lipids involved in the metabolism of glucosylceramide (a GBA substrate) have also been investigated, and interestingly, in the absence of mutations in GBA the levels of some ceramide species were higher in PD-MCI or PDD than in PDCN patients.[73]

Regarding urine, only UA has been studied to date and in keeping with findings in plasma, low UA levels are associated with poor neuropsychological performance.[57]

In summary, the fact that cognitive outcomes are associate with neurotrophic factors and markers of inflammation, and that a few longitudinal studies in small cohorts with early PD show that EGF,[63, 64] ILGF[65] and UA[59] may predict cognitive decline, suggest that these proteins could be useful as biomarkers of dementia in PD. The differences in some lipids between groups of PD patients with distinct cognitive states may also be of potential value.[70, 73] These findings are in keeping with recent data linking neurodegeneration and aging with disturbances in lipid metabolism[74, 75] and neuroinflammation.[76]

GENETIC BACKGROUND

Genes are part of our inborn biological fingerprint and although they can be useful to predict outcome (i.e .risk of dementia) they are not useful to track disease course (i.e. cognitive evolution in a patient with PD). Thus, genetic factors are better considered as "predictive markers" rather than true biomarkers. Genes related to the aggregated proteins encountered in the brain of PDD patients[9-13] (Table 2) have been extensively pursued. The ε4 allele of apolipoprotein E gene (*APO*E) is associated with increased amyloid plaque load[77] and it was found to be more prevalent in PDD than in PDND patients,[78-81] as well as being associated with lower performance in memory,[82, 83] working memory, executive function and semantic fluency[83] in PDND. However, such results were not evident elsewhere,[31, 84-90] this discrepancy probably being due to the significant methodological variability among the studies (Table 2). Most of these cross-sectional studies have been pooled in one meta-analysis,[91] suggesting an over-representation of *APOE* ε4 carriers

amongst PDD patients. In addition, although not uniformly,[22, 89, 91] longitudinal studies show that *APOE* ε4[92-95] and *APOE* ε2[94, 95] are associated with more rapid cognitive decline and a risk of PDD. In relation to the tau gene (*MAPT)*, despite the absence of uniform data,[83, 88, 92] the H1 haplotype in PD patients was found to be associated with dementia[96] and with a higher risk of progression to dementia[97] and cognitive decline[98] in the most extensive cross-sectional[96] and longitudinal studies.[97, 98] In addition, in PDND patients the H1/H1 genotype was associated with poor visual and memory outcomes,[92, 99] although this finding was not replicated in a larger study.[83] Duplications, triplications[100, 101] and some mutations of the *SNCA* gene that encodes the α-synuclein protein[102, 103] are associated with early onset dementia, although patients with idiopathic PDD and PDND did not show different polymorphisms of this gene.[104] Interestingly, a recent multicenter study in a large cohort of PD patients, show that the *APOE* ε4 allele but not the *MAPT* and *SNCA* genes was associated with lower cognitive performance.[83]

Table 2. Summary of genetic studies assessing*APOE*, *MAPT* and *GBA* as potential biomarkers of PD-MCI and PDD.

AUTHOR	PATIENTS				COGNITIVE EVALUATION / DIAGNOSTIC CRITERIA	MAIN RESULTS / FINDINGS
	PDND	PDD	PD-MCI	Controls		
***APOE* CROSS-SECTIONAL**						
Koller et al., 1995[84]	61	52			DRS / PDD by NINCDS	No differences
Parsian et al., 2002[85]	250	34		96	MMSE / PDD by McKhann et al., 1984	
Camicioli et al., 2005[86]	19	28			MMSE / PDD by DSM-IV	
Jasinska-Myga et al., 2007[87]	100	98			MMSE, attention and working memory, executive, memory, language, visuospatial / PDD byICD-10 and DSM-IV	
Ezquerra et al., 2008[88]	138	86		91	NA / PDD by MDS Task Force	
Beyer et al., 2013[31]	73*		18		MMSE, executive, memory, visuospatial / PD-MCI if cognitive performance < 1.5 SDs below predicted level	
Feldman et al., 2006[79]	49	38			NA / DSM-IV	*APOE*ε4 associated with PDD
Tröster et al., 2006[90]	62			146	DRS, attention and working memory, executive, memory, language	Absence of *APOE*ε4 associated with working memory impairment
Pankratz et al., 2006[80]	274	50			PDD by MMSE with education-specific cutoff	*APOE*ε4 associated with PDD
Papapetropoulos et al., 2007[81]	33	39			PDD by American Psychiatric Association 1987,1994 or MMSE < 24	*APOE*ε4 associated with PDD
Blazquez et al., 2006[78]	276	212			MMSE / PDD if < 24	*APOE*ε4 associated with cognitive impairment in familial PD
Mata et al., 2014[83]	1079**				MOCA, attention and working memory, executive, memory, language, visuospatial	*APOE*ε4 associated with ↓ memory, executive function, attention and language.
***APOE* LONGITUDINAL**						
Harhangi et al., 2000[95]	79	25		4673	PDD by DSM-III-R	*APOE*ε2 and APOE ε4 ↑ risk of PDD
De Lau et al., 2005[94]	139				MMSE / PDD by DSM-III-R	*APOE*ε2 and APOE ε4 ↑ risk of PDD
Kurz et al., 2009[89]	95			73	MMSE / PDD by DSM-IV	*APOE* not associated with cognitive performance at baseline or annual decline
Williams-Gray et al., 2009[91]	101				MMSE, executive, memory, language / PDD byMMSE ≤ 24 and DSM-IV	No differences
Siderowf et al., 2010[22]	45				DRS-2 / PDD if < 124	*APOE*ε4 not associated with cognitive decline

Morley et al., 2012[92]	212			DRS-2	*APOE*ε4 associated with cognitive decline
***MAPT* CROSS-SECTIONAL**					
Ezquerra et al., 2008[88]	138	86	91	PDD by MDS Task Force	No differences
Mata et al., 2014[83]	1079**			MOCA, attention and working memory, executive, memory, language, visuospatial	No association with cognitive performance
Setó-Salvia et al., 2011[96]	2154	48	374	DRS / PDD by DSM IV-R	PDD vs. C: ↑ frequency of H1. rs1467967-A allele and haplotype H2a (del-In9 variant) ↓ in PDD
***MAPT* LONGITUDINAL**					
Goris et al., 2007[98]	109**			MMSE	H1/H1 ↑ cognitive decline
Williams-Gray et al., 2009[97]	126			MMSE, executive, memory, language / PDD by MMSE ≤ 24 and DSM-IV	H1/H1 predictor of cognitive decline over 5.2 years
Morley et al., 2012[92]	212**			DRS-2, attention, memory, initiation-perseveration, construction, and conceptualization	H1/H1 associated with ↓ memory at baseline, but not with changes over time
***GBA* CROSS-SECTIONAL**					
Alcalay et al. 2010[107]	699			MMSE, Self-report of cognitive impairment	Association with self-reported cognitive impairment
Setó-Salvia et al., 2011[96]	225*		186	Clinical Dementia Rating Scale / PDD by DSM IV-R	Association with PDD
Alcalay et al., 2012[106]	72*			MMSE, CDR, executive, memory, visuospatial	Association with ↓ memory and visuospatial function
***GBA* LONGITUDINAL**					
Winder-Rhodes et al., 2013[109]	121			MMSE / PDD by DSM IV	Associated with progression to PDD
Brockmann et al., 2015[108]	39			MOCA	Associated with ↑ cognitive decline

Abbreviations. NA, Not Available. ***Genes****: APOE*, Apolipoprotein E; *MAPT*, Microtubule Associated Protein Tau; *GBA*, Glucocerebrosidase. ***Subjects:*** PDND, Parkinson's disease non-demented; PDD, Parkinson's disease dementia; PD-MCI, Parkinson's disease mild cognitive impairment; PDCN, Parkinson's disease cognitively normal; C, control. ***Cognitive assessment***: DRS, Mattis Dementia Rating Scale; DRS-2, Mattis Dementia Rating Scale (version 2); NINCDS, National Institute of Neurological Disorders and Stroke; MMSE, Mini Mental State Examination; MOCA, Montreal Cognitive Assessment; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; MDS, Movement Disorders Society.

* PD cognitively normal
** PD (the cognitive status is not specified)

Recently, a higher prevalence of dementia,[105, 106] MCI,[106] and poor outcomes in global cognition,[107] memory and visuospatial function[106] was observed in PD patients carrying *GBA* mutations. Moreover, *GBA* mutations are associated with greater cognitive decline[108] and development of PDD[109] in longitudinal studies, and with higher high LB burden.[110] It has been postulated that the poorer lysosomal activity linked to *GBA* mutations could reduce the turnover of α-synuclein through chaperone mediated autophagy, leading to LB formation.[110]

Genes related to defective neurotransmission relevant to cognition in PD have also been studied. In relation to dopamine metabolism, the Val158Met polymorphism of the catechol-o-methyl transferase (*COMT*) gene is associated with poor performance in executive function or attention[92, 111-115] but apparently, not with dementia.[97] No studies have assessed genes related to acetylcholine metabolism in PDD or PD-MCI patients, and no association between polymorphisms in the *CHRNA4* gene (the nicotinic receptor subunit alpha-4) and cognition have been encountered in PDCN patients.[116] Similarly, an association between genes related to the metabolism of homocysteine and cognition in PD has not been observed.[48, 51] Conversely, polymorphisms in the IL-17A[117] and BDNF genes [118 119] have been associated with poorer global cognition[119] and delayed recall.[118]

In summary, although there are contradictory results regarding the *APOE* ε4 allele and the H1 haplotype of the *MAPT* gene, methodological issues (i.e. differences in the size of the cohorts studied, the cognitive assessment and diagnostic accuracy for dementia and MCI, disease duration, the age of the patients, etc.) impair making comparisons between them. Meta-analysis of cross-sectional studies[91] and longitudinal studies with larger cohorts[92, 94, 95, 97] suggest that these genetic variants can be considered risk factors for dementia in PD. More recently, GBA mutations emerged as the strongest genetic predictive marker of

dementia.[105, 106, 108, 109] These genetic variations may account for, or have a great impact on, the subtype of PD-MCI and the risk of dementia.

MAGNETIC RESONANCE IMAGING (MRI)

Gray matter changes

Several cross-sectional studies have demonstrated higher brain atrophy in PDD and PD-MCI patients (more extensive in PDD) than in control subjects, PDCN or PDND,[31, 120-153] particularly in the parietal, occipital, temporal and frontal lobes, yet also in the hippocampus, amygdala, caudate, putamen, thalamus and substantia innominata (Figure 1). As expected, PDD patients had less gray matter (GM) volume than PD-MCI patients in several temporal and prefrontal areas,[137] including the amygdala,[123] and they had reduced cortical thickness in the anterior cingulate, entorhinal and orbitofrontal cortices, as well as in the parahippocampus, temporal pole, precuneus, and fusiform and lingual areas.[121] Interestingly, several studies report correlations between different areas of GM loss and cognitive function,[31, 121, 123, 127, 131, 134, 142, 146, 150, 154-162] although in terms of biomarkers of dementia and MCI, longitudinal studies are much more valuable. Thus, reduced cortical thickness in the right precentral and superior frontal gyri, as well as in the anterior cingulate cortex,[21] and less GM volume in the prefrontal areas, insular cortex and caudate nucleus,[163] along with hippocampal atrophy, were observed in PD patients who developed dementia during follow-up.[164] Interestingly, hippocampal volume was also a major factor predicting the development of MCI in PD patients,[164] and a sophisticated analysis using Bayesian network classifiers showed that PDD, PD-MCI and PDND patients were classified on this basis with high sensitivity and specificity.[165] In this study, reduced GM in the left hippocampus and right entorhinal cortex, and enlargement of the lateral ventricles identified PDD patients, and brainstem and left hippocampus atrophy was seen in PD-MCI patients.[165]

In summary (Figure 1), although there are many studies in this field, the most valuable are those with larger cohorts [31, 122, 131, 138, 142, 152, 153, 158] and more advanced analytic approaches[121, 125, 148, 152, 157, 165], especially the longitudinal studies,[21, 152, 163, 164] Accordingly, reduced cortical volume or thickness in several areas, and especially in the hippocampus,[164] appears to be associated with progression to dementia and MCI. This is a promising avenue to be followed, whereby well-designed prospective studies using modern analytical models might help to validate these findings or identify new patterns that could serve as potential biomarkers.

White matter microstructure: Diffusion Tensor Imaging

Reduced fractional anisotropy (FA) or increased mean diffusivity (MD) in diffusion tensor imaging (DTI) studies can indicate alterations in the microstructure of WM tracts. Both approaches show that dementia and MCI in PD are associated with extensive areas of modified WM microstructure (Figure 1).[153, 166-172] Reduced FA is widespread in PDD compared with PDND patients or controls, compromising the main tracts (the superior and inferior longitudinal, inferior fronto-occipital and uncinate fasciculi, the cingulum, the anterior limb of the internal capsule, and the hippocampus).[153, 166-170] In PD-MCI patients, the superior longitudinal, inferior fronto-occipital and uncinate fasciculi, as well as the cingulum, corpus callosum and corona radiata had a lower FA than in PDCN or control subjects.[153, 166, 169, 171] Notably, while PDD patients had reduced GM volume and FA, PD-MCI subjects only showed FA abnormalities in the main WM tracts,[153] suggesting that tract damage may precede GM atrophy. Regarding MD, results are analogous to those found in FA for both PD-MCI and PDD patients.[166, 168, 172] On the other hand, both FA

and MD values have been correlated with cognitive outcomes,[153, 161, 167-170, 172-175] possibly indicating a role in the detection of subtypes of cognitive failure associated with PD. Overall, the corpus callosum,[153, 171] corona radiata,[166, 171] and the inferior and superior longitudinal fasciculi are the areas most consistently altered in PDD and PD-MCI patients.[153, 166, 171] The fact that in absence of GM changes, PD-MCI patients exhibited alterations in the main WM tracts[153] suggests that DTI studies might help in the early diagnosis of cognitive decline. Longitudinal studies are not currently available and they will be needed to determine whether any of these changes may be considered as true biomarkers of MCI or dementia in PD.

Functional MRI: Cerebral blood flow

Functional MRI (fMRI) in resting state or during the execution of tasks indirectly measures neural activity and is used to study the regional activation of the brain and the association or dependency between two or more anatomic locations, termed functional connectivity. During the execution of working memory or executive function tasks, PD-MCI patients more weakly recruit the anterior cingulate cortex, caudate, medial and dorsolateral prefrontal cortex (DLPFC), and left precentral gyrus than PDCN patients.[176-178] However, similar findings were observed in PDCN patients when compared with controls[179] suggesting that these changes are associated with executive dysfunction in PD.[180, 181] Interestingly, genetic variants in PDND patients are associated with reduced recruitment of specific brain areas when executing certain tasks: the *MAPT* H1 haplotype in parietal[115] and medial temporal[99] regions when performing visuospatial and memory tests;[99] *APOE* ε4 allele in the temporo-parietal network in relation to memory encoding;[115] and *COMT* met/met homozygosity of the Val158Met polymorphism in the prefrontal cortices, frontoparietal network and caudate nuclei when executing frontal tasks.[111, 113, 115]

In the resting state, reduced inter-regional correlations have been encountered in PDD (caudate nucleus-posterior cingulate cortex/precuneus[182] and inferior occipital-right parahippocampal gyri[172, 183]) and in PD-MCI (long range connections)[184, 185] patients. In addition, reduced connectivity in the frontoparietal network is associated with poor cognitive outcome in PD-MCI,[186] and progressive loss of functional connectivity in posterior parts of the brain was associated with cognitive decline in the only longitudinal study available.[187] One interesting approach is to study the default network that reflects the predominant activity at rest, which is dampened when switching to a cognitive task. In PDD patients, this network has weaker connectivity in the right inferior frontal gyrus[188] and is less intensely deactivated than in controls when confronted with a complex visual task.[183]

Considering the data available (Figure 1), it can be speculated that there are two main functional networks in the resting state: one more anterior one that seems to be related to executive dysfunction; and another more posterior one that might herald the evolution to dementia.[187] Activation studies indicate that fMRI might be helpful in the diagnosis of PD-MCI subtypes, which may also complement studies of genetic predictive markers in patients.

Proton magnetic resonance spectroscopy: metabolite spectra

Proton magnetic resonance spectroscopy (PMRS) allows certain metabolites to be quantified *in vivo*, reflecting the integrity of different elements in the brain, such as N-acetyl aspartate (NAA, neurons), choline compounds (Cho, cell membranes) and creatine (Cr, energy metabolism).[189] PDD patients have less NAA[190] and PD-MCI patients a lower NAA/Cr ratio[191] than PDND patients in the occipital lobe, which correlates with poorer

visuospatial and working memory function.[190] In addition, PDD[191] and PD-MCI[189] patients had lower respective NAA/Cr and Cho/Cr ratios in the cingulate cortex than controls. Moreover, levels of NAA were reduced in the DLPFC of PD-MCI patients and in the hippocampus of PDD patients,[192] and they were positively correlated with frontal tasks and language function,[192] respectively. A correlation between the NAA/Cr ratio in the anterior cingulate cortex with short-term memory,[193] and with executive function and perception, [194] has also been observed. Finally, the inorganic phosphate/ATP ratio, a measure of oxidative metabolism, was negatively correlated with global cognition and language in PDND patients.[195] Longitudinal studies are needed to decipher whether the biochemical alterations described might predict conversion to dementia or identify subtypes of PD-MCI.

In summary, despite the number of studies undertaken with MRI, no reliable biomarker of dementia has been identified. From the information provided by the different MRI modalities in the few longitudinal studies available, the most consistent conclusion points to the fact that a lower hippocampal volume and dysfunction of the posterior-hippocampal network, witnessed either by fMRI or spectroscopy, might signal the eventual development of dementia. Nevertheless, their value at the individual level has to be further explored.

PET AND SPECT IMAGING

Dopaminergic denervation

Several studies have identified dopaminergic deficits in the striatum, anterior cingulate and midbrain in PDD patients, and in the striatum and the insula of PD-MCI patients compared with PDCN patients.[176, 196-199] However, in all types of patients (PDCN, PD-

MCI and PDD) these deficits are associated with poor executive function, especially those in the striatum,[176, 200-206] and less consistently with verbal and visual memory[126] or global cognition.[196] In addition, several studies failed to find an association between dopamine depletion and cognitive impairment.[207-209] Therefore, the assessment of the dopaminergic system with these imaging techniques could serve as a biomarker of executive PD-MCI, an important entity with implications for functional performance. However, this does not seem to be sufficiently reliable to serve as a biomarker of dementia or MCI.

Cholinergic denervation

Pathological studies[210] and pharmacological trials with acetylcholinesterase inhibitors[211] indicate that the cholinergic disfunction is relevant in dementia in PD. Studies using different radiotracers (Supplementary Table 2), show that the cholinergic activity in PDD patients was weaker in the whole cortex,[212-214] and in the occipital,[213] precentral, parietal, temporal and posterior cingulate cortex[215] than in PDND and healthy subjects.[216, 217] Compared with controls, cholinergic deficits were evident in the midbrain, pons and cerebellum in one study of PD-MCI patients[218] but not in another that included more patients.[198] In addition, lower cortical cholinergic activity has been associated with worse global cognition[219, 220] and language,[221] and with working memory impairment in PDD and PDND patients.[217]

PET studies indicate that assessing the cholinergic state might be useful as a biomarker of dementia in PD. Despite the evidence available, the current accessibility of the radiotracers precludes more extensive research and the clinical use of this technique.

Supplementary table 2. Summary of PiB PET and acetylcholine-related PET and SPECT studies assessing PD-MCI or PDD and those reporting correlations with any cognitive measure in PD, PDND or PDCN.

	AUTHOR AND YEAR	**PATIENTS**	**COGNITIVE EVALUATION / DIAGNOSTIC CRITERIA**	**MAIN RESULTS**
[^{11}C]-PIB PET *Amyloid load*	Maetzler et al., 2008[225]	PDD (n=10) C (n=6)	MMSE / PDD by DSM-IV	2/10 PDD ↑ uptake in cortical areas
	Edison et al., 2008[222]	PDND (n=10) PDD (n=12) C (n=41)	MMSE / PDD by MDS Task Force	2/12 PDD ↑ uptake
	Maetzler et al., 2009[20]	PDND (n=14) PDD (n=12)	MMSE / PDD by DSM-IV	4/12 PDD ↑ uptake in the frontal, posterior cingulate, cuneus/precuneus, temporo-parietooccipital cortices and striatum
	Burack et al., 2010[226]	PDD (n=3)	MMSE, CDR / PDD by MDS Task Force	2/3 autopsy confirmed PDD ↑ uptake in orbitofrontal, prefrontal cortex, precuneus and temporal lobes
	Foster et al., 2010[229]	PDCN (n=8) PD-MCI (n=9) PDD (n=15) C (n=9)	CDR, attention and working memory, executive, memory, language, visuospatial / PDD by MDS Task Force; PD-MCI if CDR=0.5	No differences
	Jokinen et al., 2010[253]	PDND (n=8) PDD (n=11)	MMSE, attention and working memory, executive, memory / PDD by MDS Task Force	3/11 PDD and 2/24 C ↑ uptake in cortical areas
	Gomperts et al., 2012[228]	PDCN (n=29) PD-MCI (n=14) PDD (n=12) C (n=85)	MMSE, CDR, attention and working memory, executive, memory, language, visuospatial / PDD by MDS Task Force; PD-MCI if one abnormal aggregate cognitive domain score -1.5 SD	No differences
	Petrou et al., 2012[224]	PDNC (n=5) PD-MCI (n=30) PDD (n=5)	MOCA, attention and working memory, executive, memory, visuospatial / PD-MCI based on domain Z-scores (not specified)	4/5 PDD and 2/30 PD-MCI ↑ cortical uptake. Negative correlation between cortical binding and global cognition
	Gomperts et al., 2013[230]	PDNC (n=35) PD-MCI (n=11) *Longitudinal (2.5±1.4 years follow-up)*	MMSE, attention and working memory, executive, memory, language, visuospatial /PD-MCI by Winblad et al., 2004	PD-MCI vs. PDCN: At baseline no differences Longitudinal course: Subjects progressing to a more severe cognitive diagnosis (n=14) ↑ baseline uptake
	Campbell et al., 2013[227]	PDD (n=53) C (n=67)	MMSE, CDR / PDD by MDS Task Force	PDD vs. C: No differences
	Shimada et	PDD (n=7)	MMSE, executive / PDD	29% of PDD ↑ uptake. No correlations between

	al., 2013[223]	C (n=17)	by DSM-IV	uptake and neuropsychological tests
	Lucero et al., 2015[231]	PDND (n=130) PDD (n=15)	MMSE, CDR / PDD defined by CDR	Uptake correlated with cognition in patients with <16 years of education
[^{11}C]-PMP PET *Acetylcholinesterase activity*	Bohnen et al., 2003[216]	PDND (n=11) PDD (n=14)	MMSE / PDD by DSM-IV	AChE activity ↓ in PDD (-20%) and in PDND (-12.9%) vs. controls
	Bohnen et al., 2006[217]	PDND (n=13) PDD (n=11) C (n=14)	MMSE / PDD by DSM-IV	PDD vs. C: ↓ cortical AChE activity PDD+PDND: Cortical AChE activity correlated with attention.
	Shimada et al., 2009[213]	PDND (n=18) PDD (n=10) C (n=26)	MMSE / PDD by DSM-IV	PDD vs. PDND↓ AChE activity in the inferior temporal, supramarginal, and posterior cingulate gyri.
	Bohnen et al., 2012[219]	PD (n=101) C (n=29)	MMSE, attention and working memory, executive, memory, visuospatial / PDD by DSM-IV	↓ cortical AChE activity, associated with ↓ in verbal learning, executive function, and attention
	Bohnen et al., 2015[220]	PDND (n=143)	MMSE, attention and working memory, executive, memory, visuospatial / Not reported	↓ cortical AChE activity in PDND with worse cognitive outcome
2-[^{18}F]FA-85380 PET *α4β2* nicotinic acetylcholine receptors*	Meyer et al., 2009[218]	PDCN (n=7) PD-MCI (n=8) C (n=9)	MMSE, DemTecscale, attention and working memory, executive, memory, visuospatial / PD-MCI defined if DemTecscale=8-13	PD-MCI vs. PDCN: ↓ midbrain, pons and cerebellum PD-MCI vs. C: ↓midbrain, pons, left parietal cortex, cerebellum
[^{11}C]-MP4A PET *Acetylcholinesterase activity*	Hilker et al., 2005[215]	PDND (n=17) PDD (n=10)	MMSE, attention and working memory, executive, memory, language, visuospatial / PDD by DSM-IV	PDD vs. PDND: ↓ left inferior parietal lobe, left precentral gyrus and right posterior cingulate gyrus
	Klein et al., 2010[212]	PDND (n=8) PDD (n=9) C (n=9)		
[^{123}I]IBVM SPECT *Presynaptic cholinergic terminal density*	Kuhl et al. 1996[214]	PDND (n=9) PDD (n=6) C (n=36)	CDR / PDD by CDR 0.5 or clinical data	PDD vs. PDND: ↓ extensive cortical uptake
5-I-A-85380 SPECT *α4β2* nicotinicacetylcholinereceptors*	Lorenz et al., 2014[221]	PD (n=25)	Language	Correlation between language performance and uptake in right superior parietal lobule, left thalamus, posterior subcortical region

Abbreviations. ***PET/SPECT technique****:* PiB, Pittsburgh compound B; PMP, Methyl-piperidin-4-yl propionate; FA-85380, 3-((S)-2-azetidinylmethoxy)pyridine; MP4A, Methylpiperidin-4-yl acetate; IBVM, Iodobenzovesamicol; A-85380, 5-iodo-3-[2(S)-azetidinylmethoxy]pyridine. ***Subjects:*** PDND, Parkinson's disease non-demented; PDD, Parkinson's disease dementia; PD-MCI,

Parkinson's disease mild cognitive impairment; PDCN, Parkinson's disease cognitively normal; C, control.***Cognitive assessment:*** CDR, Clinical Dementia Rating of Hughes et al., 1982; MMSE, Mini Mental State Examination; MOCA, Montreal Cognitive Assessment; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MDS, Movement Disorders Society.

Imaging amyloid

Fibrils of Aß can be assessed *in vivo* by [^{11}C]-Pittsburgh compound B (PiB) PET imaging. From the few such studies undertaken in PD patients (Supplementary Table 2), 15-80 % of PDD cases[20, 222-226] and only 2 out of 30 PD-MCI patients had elevated cortical PiB binding.[224] Although no differences were evident between PDD and controls[227-229] or between PD-MCI and PDCN patients in several studies,[228, 229] higher PiB retention in PD-MCI patients predicted a greater risk of cognitive worsening.[230] In addition, a robust correlation between global cognition and PiB binding was observed in PDCN, PD-MCI and PDD patients.[224, 231] Therefore, while it can be argued that amyloid load might contribute to the development of cognitive impairment in PD,[10, 14, 232] the *in vivo* results of PiB-PET studies are rather variable,[233] with low sensitivity and specificity in the diagnosis of dementia and MCI in PD patients. Nonetheless, the paucity of studies and the heterogeneity in the cognitive deficits of PDD and PD-MCI patients could explain these inconsistent findings. As mentioned for other biomarkers related to Aß, PiB-PET might represent a useful biomarker for specific types of PDD with concurrent AD but not for all types of PDD (e.g. purer Lewy body type cases). Another factor to be considered is that PiB retention in PDD patients seems to be related to diffuse Aß plaques and not to mature plaques, which are not associated with AD but with pathological aging.[226]

Imaging brain perfusion and metabolism

Regional cerebral blood flow (rCBF) and glucose consumption (FDG uptake - metabolism) can be measured by SPECT and PET respectively (Figure 2). In several studies PDD and PD-MCI patients exhibit areas of reduced rCBF[234-249] and metabolism (more extensive in PDD),[212, 250-258] such as in the frontal, parietal, temporal, occipital and cingulate cortex, the basal ganglia, thalamus and cerebellum. Interestingly, compared to PD-MCI, hypometabolism is more widespread in PDD patients, especially in the posterior cortical areas,[251] and this heralds the progression to dementia in PD patients when considered in conjunction with the hypometabolism in the posterior cingulate and caudate nucleus.[259, 260] Moreover, impairment in specific cognitive domains is correlated with patterns of rCBF and hypometabolism in several studies.[235, 251, 261-267]. Furthermore, a recent study in a cohort of PDD patients with a multimodal PET approach show a correlation between hypometabolism, amyloid load and microglial activation ([^{11}C]-(R)PK11195 PET) in the anterior and posterior cingulate, striatum and frontal, temporal, parietal and occipital cortical regions.[250]

In summary, reduced rCBF and FDG uptake in the posterior cortical areas seems to be a useful biomarker of dementia in PD,[251] in line with functional and spectroscopic MRI data.[187, 190] In addition, considering the heterogeneity of PD-MCI, a multi-tracer approach might be worth studying to decipher biomarkers of MCI that could eventually develop into dementia.

NEUROPHYSIOLOGY

Electroencephalography (EEG) and magnetoencephalography

PDD patients have slow EEG activity,[268-271] with an increase in power at the delta (1-4 Hz) and theta (4-8 Hz) frequencies.[272-274] In addition, PD-MCI patients have increased

activity in the theta band in the frontal region[275] and reduced alpha activity (8-10 Hz) in the right temporal region[276] compared with PDCN patients. Moreover, PDND patients with a low background rhythm frequency had a higher ratio of progression to dementia[277] or global cognitive decline,[278] and low background EEG frequencies have also been associated with poor outcomes in global cognition,[279, 280] attention, executive function, verbal fluency and long-term memory.[281, 282]

Although expensive and with restricted accessibility, another way to measure cortical neuron activity is magnetoencephalography, which provides a measure of rhythmic activity and of the synchronization of oscillatory activity over long distances with higher temporal resolution. In addition to a widespread increase in the relative power of the delta band, and a decreased power of the alpha and beta bands,[283] PDD patients have reduced long distance intra-hemispheric bilateral fronto-temporal and inter-temporal synchronization.[284] As such, current evidence indicates a clear association between low frequency oscillatory activity and cognitive impairment. Thus, the use of novel analytical EEG approaches should be considered in the search for biomarkers of dementia in PD, particularly as they are cheap and easy to employ.

Event-related potentials

Event-related potentials (ERPs) involve cortical responses associated with sensory, motor or cognitive events,[285] in which later components (after 100 ms) are thought to reflect cognitive processing. The most widely studied in PD is the P3 or P300 (elicited by visual or auditory stimuli), which appears to be delayed in PDD compared with controls[286-289] or PDND patients.[290, 291] Indeed, P300 correlates with many cognitive functions in PDND patients like memory, visual perception and executive functions.[292-296] A recently developed transcranial

magnetic stimulation (TMS) method that is coupled to simultaneous peripheral nerve stimulation at different intervals can produce short latency afferent inhibition (SAI), which is thought to provide a measure of cholinergic function. Several studies show that SAI is dampened in patients with PDD[297] and PD-MCI,[298] while there is no difference in SAI between PDCN and control subjects. Due to the relevance of the cholinergic system in the cognitive deficits in PD, this is a promising technique to be considered in the search for biomarkers of PD-MCI with higher risk of dementia.

CONCLUSIONS AND FUTURE DIRECTIONS

An important factor to consider when evaluating the potential biomarkers studied is the fact that dementia and MCI in PD are heterogeneous, both from the clinical and the pathological perspective. In addition, different biomarkers may provide complementary information that could be combined to achieve better sensitivity and specificity in the detection of dementia, and MCI with a high risk of progressing to dementia (Table 3). The data currently available indicate that genetic information could aid the detection of PD patients at a high risk of dementia at the time of diagnosis, yet this sheds no light on the probability and the time lag in this cognitive decline. By contrast, other biomarkers aim to prematurely detect dementia during the evolution of the disease and they could be especially useful to flag those PD-MCI patients at high risk of developing dementia in the short- to mid-term.

Table 3. Summary of the potential biomarkers of PDD and PD-MCI in function of the pathological processes implicated.

BIOMARKER	CSF		PLASMA		GENES		PET/SPECT IMAGING	
	PDD	PD-MCI	PDD	PD-MCI	PDD	PD-MCI	PDD	PD-MCI
PATHOLOGY-RELATED								
Amyloid-ß[¥]	↓/=	↓/=	---	---	↑ *APOE*ε4*	---	↑PiB uptake/=	↑PiB uptake/=
Tau[¥]	↑/=	↑/=	---	---	↑H1 haplotype and H1/H1 genotype/ No association	---	---	---
P-tau	↑/=	↑/=	---	---			---	---
α-synuclein	↑/=	---	---	---	Duplication, triplication	---	---	---
NEUROTRANSMITTER DYSFUNCTION								
Dopamine	---	---	---	---	=	---	↓ subcortical DaT or fluorodopa uptake/=	↓ subcortical DaT or fluorodopa uptake /=
					COMT (Val158Met) associated with ↓ executive function in PDND			
Acetilcholine	---	---	---	---	---	---	↓ cortical AChE activity/=	---
INFLAMMATION/INMUNE RESPONSE								
CRP	↑	---	=	---	---	---	↑ microglial activation in the cingulate, striatum, frontal, temporal, parietal and occipital cortices	---
IL-1β	---	↑	---	---	---	---		
IL-6[¥]	=	↑	---	---	---	---		
IL-17A	---	---	---	---	Genotype C/C of the rs8193036 polymorphism;MMSE < 26	---		
IL-10	---	---	---	---	Polymorphism RS1800896; no association	---		
TNF- α[¥]	=	↓	---	---		---		
INF-γ	---	↓	---	---	Polymorphism T874A; no association	---		

PGE_2	---	=	---	---	---	---		
IP10	=	---	---	---	---	---		
MIP1β	=	---	---	---	---	---		
MCP1	=	---	---	---	---	---		
OXIDATIVE STRESS								
Uric acid[δ, ¥]	↓	---	=	---	---	---	---	---
NEUROTROPHIC/NEUROPROTECTION								
EGF[¥]	---	---	↓	---	---	---	---	---
BDNF	=	---	---	---	PolymorphismVal196Met; no association	---	---	---
Vitamin D	---	---	=	---	---	---	---	---
OTHER								
Homocysteine[¥]	↑/=	=	↑/=	=	Variants in MTHFR, COMT and other genes related to homocysteine metabolism; no association		---	---

Abbreviations "=", No differences. ***Biomarkers:*** CRP, C reactive protein; IL-1β, Interleukin-1β; IL-6, Interleukin-6; L-17A, Interleukin 17A; IL-10, Interleukin 10; TNF-α, Tumor necrosis factor alpha; IFN-γ, Interferon gamma; PGE_2, Prostaglandin E_2; IP10, Interferon gamma-induced protein-10; MIP1β, Macrophage inflammatory protein-1; MCP1, Monocyte chemotactic protein-1; EGF, Epidermal Growth Factor; BDNF, Brain Derived Neurotrophic Factor; PiB, Pittsburgh Compound B. ***Subjects:*** PDND, Parkinson's disease non-demented; PDD, Parkinson's disease with dementia; PD-MCI, Parkinson's disease with mild cognitive impairment.

*APOE encodes for apolipoprotein E, and it is associated with the cerebral Amyloid-ß load
[δ]Low urine uric acid levels associated with worse performance in several cognitive outcomes
[¥]Association with cognition in PDND, PD-MCI or PDD

The data available allow us to conclude that genetic variants in *COMT* may account for differences in frontal dopaminergic function, they are typically associated with an executive subtype of PD-MCI with a low risk of dementia.[92, 97, 111-115] By contrast, the *APOE* ε4 allele,[92, 94, 95] the H1 haplotype of the *MAPT* gene[97, 98] and mutations in the GBA gene[109] all seem to be risk factors of dementia. However, they might be associated with different PD-MCI subtypes and probability of progression to dementia with slightly different cerebral pathology. Indeed, even in PDCN patients these mutations are associated with deficient activation in restricted brain territories when confronted with specific cognitive tests.[99, 111, 113, 115] Thus, *APOE* ε4 might be associated with a more amnestic AD-like phenotype of PD-MCI, while *MAPT* and *GBA* might be involved in more visuospatial patterns.

Regarding the proteins related to pathological cerebral inclusions, currently only low Aß levels in the CSF and PiB PET studies detecting Aß fibrils in the brain could have some potential to detect early dementia among PD-MCI patients. This could reflect a subgroup of patients with concurrent AD or AD pathological changes in whom the *APOE* ε4 allele might be also overrepresented. In this sense, these markers might not be useful for the purer LB cases of PDD, which could in turn be more related to *GBA* mutations.[108-110] Oligomers of α-synuclein in the CSF are worth pursuing, both in sporadic PD but importantly, also in patients with *GBA* mutations. In addition, the ratios of tau, Aß and α-synuclein could improve the predictive value of each protein independently, or help to differentiate between different forms of PD-MCI. New PET radiotracers to reliable mark *in vivo* tau and α-synuclein are needed to derive a complete picture of the clinical and pathological phenotypes of MCI subtypes, and how they progress towards dementia.

In addition, independently of the genetic fingerprint and pathological cerebral inclusions, it may be worth pursuing the study of lipids and of proteins related to metabolic processes (inflammation, oxidative stress, etc.) in CSF or plasma/serum, as well as neurotrophic factors

putatively involved in neurodegeneration such as EGF, ILGF, UA, neurofilament light chain protein and fatty acid binding-protein.[47, 59, 63-65]. Besides their diagnostic value, these fluid biomarkers may be particularly relevant in revealing dysfunctional biological processes that might be targets for pharmacological modulation (e.g. inflammation).

On the other hand, the cerebral cholinergic deficits detected by PET also seem to be a promising biomarker of dementia[212-215, 219, 220] but due to practical issues, alternative cheap and easy ways to evaluate cholinergic function should be considered, such as new neurophysiological studies (TMS combined with ERP).[297, 298]

Pathological inclusions and neurotransmission deficits provoke neuronal dysfunction and death, which can be assessed by structural and functional imaging. Despite the fact that atrophy in structures like the hippocampus[21, 163, 164] and reduced activity/metabolism in posterior cerebral areas[187, 251,] are associated with progression to dementia, no MRI modalities or FDG-PET are sufficiently reliable as to accurately predict progression to dementia at the single-patient level, as seen in CSF and peripheral fluid studies. Similarly to what has been discussed for other biomarkers, it could be that these findings are associated with subtypes of MCI (ie. hippocampal atrophy with AD/amnestic type, and posterior dysfunction with visuospatial/LB type). The coupling of different PET studies, multimodal MRI and classic and modern neurophysiological approaches (EEG and ERP), to more sophisticated analytical methods (i.e. neuronal networks, classifiers, etc.) represents a promising approach that might give rise to new tools to identify and stratify patients with distinct types of cognitive impairment and risk of dementia.

Multidisciplinary prospective studies in large cohorts of properly classified PD-MCI patients that assess the most promising biomarkers encountered in PDD patients, are now necessary to diagnose PD-MCI patients that are at high risk of progressing to dementia. In addition, studies

in early PD patients could also allow subtypes of PD with precocious development of dementia to be identified.

Acknowledgements

Author's Roles

(1) Research Project: A, Conception; B, Organization; C, Execution.

(2) Statistical Analysis: A, Design; B, Execution; C, Review and Critique

(3) Manuscript Preparation: A, Writing of the first draft; B, Review and Critique.

M.D.-A.: 1A, 1C, 3A, 3B

B.G.: 1C, 3B

I.N.-G.: 3B

H.J.-U.: 3B

M.C.R.-O.: 1A, 1B, 1C, 3A, 3B

Financial Disclosures of all the authors (for the preceding 12 months): M.D.-A. holds a Basque Country Government Predoctoral Research Grant and has received a research award from Fundación Jesús de Gangoiti Barrera. B.G. has no disclosures. I.N.-G. receives support from CIBERNED. H.J.-U. holds a Basque Country Government Predoctoral Research Grant. M.C.R.-O. received honorarium for lectures, travel and accommodation to attend scientific meetings from UCB, and Boston Scientific, and she received financial support for her research from national and regional government bodies in Spain (Institute of Health Carlos III, Basque Country Government, Diputacion Foral Guipuzcoa, CIBERNED) and Europe.

References

1. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 2008;23(6):837-844.

2. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003;60(3):387-392.

3. 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(10):1814-1824.

4. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Mov Disord 2006;21(9):1343-1349.

5. Gasca-Salas C, Estanga A, Clavero P, et al. Longitudinal Assessment of the Pattern of Cognitive Decline in Non-Demented Patients with Advanced Parkinson's Disease. J Parkinsons Dis 2014.

6. Pedersen KF, Larsen JP, Tysnes OB, Alves G. Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. JAMA Neurol 2013;70(5):580-586.

7. Broeders M, de Bie RM, Velseboer DC, Speelman JD, Muslimovic D, Schmand B. Evolution of mild cognitive impairment in Parkinson disease. Neurology 2013;81(4):346-352.

8. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27(3):349-356.

9. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Ann Neurol 2005;58(5):773-776.

10. Sabbagh MN, Adler CH, Lahti TJ, et al. Parkinson disease with dementia: comparing patients with and without Alzheimer pathology. Alzheimer Dis Assoc Disord 2009;23(3):295-297.

11. Braak H, Rub U, Jansen Steur EN, Del Tredici K, de Vos RA. Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 2005;64(8):1404-1410.

12. Compta Y, Parkkinen L, O'Sullivan SS, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain 2011;134(Pt 5):1493-1505.

13. Halliday GM, Leverenz JB, Schneider JS, Adler CH. The neurobiological basis of cognitive impairment in Parkinson's disease. Mov Disord 2014;29(5):634-650.

14. Adler CH, Caviness JN, Sabbagh MN, et al. Heterogeneous neuropathological findings in Parkinson's disease with mild cognitive impairment. Acta Neuropathol 2010;120(6):827-828.

15. Jellinger K. Heterogenous mechanisms of mild cognitive impairment in Parkinson's disease. J Neural Transm 2012;119(3):381-382.

16. Mollenhauer B, Trenkwalder C, von Ahsen N, et al. Beta-amlyoid 1-42 and tau-protein in cerebrospinal fluid of patients with Parkinson's disease dementia. Dement Geriatr Cogn Disord 2006;22(3):200-208.

17. Montine TJ, Shi M, Quinn JF, et al. CSF Abeta(42) and tau in Parkinson's disease with cognitive impairment. Mov Disord 2010;25(15):2682-2685.

18. Compta Y, Valente T, Saura J, et al. Correlates of cerebrospinal fluid levels of oligomeric- and total-alpha-synuclein in premotor, motor and dementia stages of Parkinson's disease. J Neurol 2015;262(2):294-306.

19. Compta Y, Ezquerra M, Munoz E, et al. High cerebrospinal tau levels are associated with the rs242557 tau gene variant and low cerebrospinal beta-amyloid in Parkinson disease. Neurosci Lett 2011;487(2):169-173.

20. Maetzler W, Liepelt I, Reimold M, et al. Cortical PIB binding in Lewy body disease is associated with Alzheimer-like characteristics. Neurobiol Dis 2009;34(1):107-112.

21. Compta Y, Pereira JB, Rios J, et al. Combined dementia-risk biomarkers in Parkinson's disease: a prospective longitudinal study. Parkinsonism Relat Disord 2013;19(8):717-724.

22. Siderowf A, Xie SX, Hurtig H, et al. CSF amyloid {beta} 1-42 predicts cognitive decline in Parkinson disease. Neurology 2010;75(12):1055-1061.

23. Liu C, Cholerton B, Shi M, et al. CSF tau and tau/Abeta42 predict cognitive decline in Parkinson's disease. Parkinsonism Relat Disord 2015;21(3):271-276.

24. Parnetti L, Farotti L, Eusebi P, et al. Differential role of CSF alpha-synuclein species, tau, and Abeta42 in Parkinson's Disease. Front Aging Neurosci 2014;6:53.

25. Compta Y, Marti MJ, Ibarretxe-Bilbao N, et al. Cerebrospinal tau, phospho-tau, and beta-amyloid and neuropsychological functions in Parkinson's disease. Mov Disord 2009;24(15):2203-2210.

26. Hall S, Ohrfelt A, Constantinescu R, et al. Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or parkinsonian disorders. Arch Neurol 2012;69(11):1445-1452.

27. Jansen Steur E, Vermes I, de Vos RA. Cerebrospinal-fluid tau protein and aspartate aminotransferase in Parkinson's disease. Lancet 1998;351(9109):1105-1106.

28. Parnetti L, Tiraboschi P, Lanari A, et al. Cerebrospinal fluid biomarkers in Parkinson's disease with dementia and dementia with Lewy bodies. Biol Psychiatry 2008;64(10):850-855.

29. Vranova HP, Henykova E, Kaiserova M, et al. Tau protein, beta-amyloid(1)(-)(4)(2) and clusterin CSF levels in the differential diagnosis of Parkinsonian syndrome with dementia. J Neurol Sci 2014;343(1-2):120-124.

30. Maetzler W, Tian Y, Baur SM, et al. Serum and cerebrospinal fluid levels of transthyretin in Lewy body disorders with and without dementia. PLoS One 2012;7(10):e48042.

31. Beyer MK, Alves G, Hwang KS, et al. Cerebrospinal fluid Abeta levels correlate with structural brain changes in Parkinson's disease. Mov Disord 2013;28(3):302-310.

32. Yu SY, Zuo LJ, Wang F, et al. Potential biomarkers relating pathological proteins, neuroinflammatory factors and free radicals in PD patients with cognitive impairment: a cross-sectional study. BMC Neurol 2014;14(1):113.

33. Alves G, Bronnick K, Aarsland D, et al. CSF amyloid-beta and tau proteins, and cognitive performance, in early and untreated Parkinson's disease: the Norwegian ParkWest study. J Neurol Neurosurg Psychiatry 2010;81(10):1080-1086.

34. Leverenz JB, Watson GS, Shofer J, Zabetian CP, Zhang J, Montine TJ. Cerebrospinal fluid biomarkers and cognitive performance in non-demented patients with Parkinson's disease. Parkinsonism Relat Disord 2011;17(1):61-64.

35. Stav AL, Aarsland D, Johansen KK, Hessen E, Auning E, Fladby T. Amyloid-beta and alpha-synuclein cerebrospinal fluid biomarkers and cognition in early Parkinson's disease. Parkinsonism Relat Disord 2015;21(7):758-764.

36. Wennstrom M, Surova Y, Hall S, et al. Low CSF levels of both alpha-synuclein and the alpha-synuclein cleaving enzyme neurosin in patients with synucleinopathy. PLoS One 2013;8(1):e53250.

37. Hansson O, Hall S, Ohrfelt A, et al. Levels of cerebrospinal fluid alpha-synuclein oligomers are increased in Parkinson's disease with dementia and dementia with Lewy bodies compared to Alzheimer's disease. Alzheimers Res Ther 2014;6(3):25.

38. Stewart T, Liu C, Ginghina C, et al. Cerebrospinal fluid alpha-synuclein predicts cognitive decline in Parkinson disease progression in the DATATOP cohort. Am J Pathol 2014;184(4):966-975.

39. Buddhala C, Campbell MC, Perlmutter JS, Kotzbauer PT. Correlation between decreased CSF alpha-synuclein and Abeta(1)(-)(4)(2) in Parkinson disease. Neurobiol Aging 2015;36(1):476-484.

40. Lindqvist D, Hall S, Surova Y, et al. Cerebrospinal fluid inflammatory markers in Parkinson's disease - Associations with depression, fatigue, and cognitive impairment. Brain Behav Immun 2013.

41. Maetzler W, Stapf AK, Schulte C, et al. Serum and cerebrospinal fluid uric acid levels in lewy body disorders: associations with disease occurrence and amyloid-beta pathway. J Alzheimers Dis 2011;27(1):119-126.

42. Maetzler W, Schmid B, Synofzik M, et al. The CST3 BB genotype and low cystatin C cerebrospinal fluid levels are associated with dementia in Lewy body disease. J Alzheimers Dis 2010;19(3):937-942.

43. Kuiper MA, Mulder C, van Kamp GJ, Scheltens P, Wolters EC. Cerebrospinal fluid ferritin levels of patients with Parkinson's disease, Alzheimer's disease, and multiple system atrophy. J Neural Transm Park Dis Dement Sect 1994;7(2):109-114.

44. Compta Y, Santamaria J, Ratti L, et al. Cerebrospinal hypocretin, daytime sleepiness and sleep architecture in Parkinson's disease dementia. Brain 2009;132(Pt 12):3308-3317.

45. Jesse S, Lehnert S, Jahn O, et al. Differential sialylation of serpin A1 in the early diagnosis of Parkinson's disease dementia. PLoS One 2012;7(11):e48783.

46. Lehnert S, Jesse S, Rist W, et al. iTRAQ and multiple reaction monitoring as proteomic tools for biomarker search in cerebrospinal fluid of patients with Parkinson's disease dementia. Exp Neurol 2012;234(2):499-505.

47. Backstrom DC, Eriksson Domellof M, Linder J, et al. Cerebrospinal Fluid Patterns and the Risk of Future Dementia in Early, Incident Parkinson Disease. JAMA Neurol 2015;72(10):1175-1182.

48. Bialecka M, Kurzawski M, Roszmann A, et al. Association of COMT, MTHFR, and SLC19A1(RFC-1) polymorphisms with homocysteine blood levels and cognitive impairment in Parkinson's disease. Pharmacogenet Genomics 2012;22(10):716-724.

49. Song IU, Kim JS, Park IS, et al. Clinical significance of homocysteine (hcy) on dementia in Parkinson's disease (PD). Arch Gerontol Geriatr 2013;57(3):288-291.

50. O'Suilleabhain PE, Sung V, Hernandez C, et al. Elevated plasma homocysteine level in patients with Parkinson disease: motor, affective, and cognitive associations. Arch Neurol 2004;61(6):865-868.

51. Rodriguez-Oroz MC, Lage PM, Sanchez-Mut J, et al. Homocysteine and cognitive impairment in Parkinson's disease: a biochemical, neuroimaging, and genetic study. Mov Disord 2009;24(10):1437-1444.

52. Hassin-Baer S, Cohen O, Vakil E, et al. Plasma homocysteine levels and Parkinson disease: disease progression, carotid intima-media thickness and neuropsychiatric complications. Clin Neuropharmacol 2006;29(6):305-311.

53. Camicioli RM, Bouchard TP, Somerville MJ. Homocysteine is not associated with global motor or cognitive measures in nondemented older Parkinson's disease patients. Mov Disord 2009;24(2):176-182.

54. Peterson AL, Murchison C, Zabetian C, et al. Memory, mood, and vitamin d in persons with Parkinson's disease. J Parkinsons Dis 2013;3(4):547-555.

55. Gonzalez-Aramburu I, Sanchez-Juan P, Sierra M, et al. Serum uric acid and risk of dementia in Parkinson's disease. Parkinsonism Relat Disord 2014;20(6):637-639.

56. Song IU, Kim YD, Cho HJ, Chung SW. Is neuroinflammation involved in the development of dementia in patients with Parkinson's disease? Intern Med 2013;52(16):1787-1792.

57. Annanmaki T, Pessala-Driver A, Hokkanen L, Murros K. Uric acid associates with cognition in Parkinson's disease. Parkinsonism Relat Disord 2008;14(7):576-578.

58. Moccia M, Picillo M, Erro R, et al. Is serum uric acid related to non-motor symptoms in de-novo Parkinson's disease patients? Parkinsonism Relat Disord 2014;20(7):772-775.

59. Moccia M, Picillo M, Erro R, et al. Presence and progression of non-motor symptoms in relation to uric acid in de novo Parkinson's disease. Eur J Neurol 2014.

60. Menza M, Dobkin RD, Marin H, et al. The role of inflammatory cytokines in cognition and other non-motor symptoms of Parkinson's disease. Psychosomatics 2010;51(6):474-479.

61. Scalzo P, Kummer A, Cardoso F, Teixeira AL. Serum levels of interleukin-6 are elevated in patients with Parkinson's disease and correlate with physical performance. Neurosci Lett 2010;468(1):56-58.

62. Rocha NP, Scalzo PL, Barbosa IG, et al. Cognitive Status Correlates with CXCL10/IP-10 Levels in Parkinson's Disease. Parkinsons Dis 2014;2014:903796.

63. Pellecchia MT, Santangelo G, Picillo M, et al. Serum epidermal growth factor predicts cognitive functions in early, drug-naive Parkinson's disease patients. J Neurol 2013;260(2):438-444.

64. Chen-Plotkin AS, Hu WT, Siderowf A, et al. Plasma epidermal growth factor levels predict cognitive decline in Parkinson disease. Ann Neurol 2011;69(4):655-663.

65. Pellecchia MT, Santangelo G, Picillo M, et al. Insulin-like growth factor-1 predicts cognitive functions at 2-year follow-up in early, drug-naive Parkinson's disease. Eur J Neurol 2014;21(5):802-807.

66. Ma J, Jiang Q, Xu J, et al. Plasma insulin-like growth factor 1 is associated with cognitive impairment in Parkinson's disease. Dement Geriatr Cogn Disord 2015;93(5-6):251-256.

67. Angelucci F, Peppe A, Carlesimo GA, et al. A pilot study on the effect of cognitive training on BDNF serum levels in individuals with Parkinson's disease. Front Hum Neurosci 2015;9:130.

68. Dexter DT, Holley AE, Flitter WD, et al. Increased levels of lipid hydroperoxides in the parkinsonian substantia nigra: an HPLC and ESR study. Mov Disord 1994;9(1):92-97.

69. Jenner P. Oxidative stress in Parkinson's disease. Ann Neurol 2003;53 Suppl 3:S26-36; discussion S36-28.

70. Li Z, Zhang J, Sun H. Increased plasma levels of phospholipid in Parkinson's disease with mild cognitive impairment. J Clin Neurosci 2015;22(8):1268-1271.

71. Pratico D. F(2)-isoprostanes: sensitive and specific non-invasive indices of lipid peroxidation in vivo. Atherosclerosis 1999;147(1):1-10.

72. Connolly J, Siderowf A, Clark CM, Mu D, Pratico D. F2 isoprostane levels in plasma and urine do not support increased lipid peroxidation in cognitively impaired Parkinson disease patients. Cogn Behav Neurol 2008;21(2):83-86.

73. Mielke MM, Maetzler W, Haughey NJ, et al. Plasma ceramide and glucosylceramide metabolism is altered in sporadic Parkinson's disease and associated with cognitive impairment: a pilot study. PLoS One 2013;8(9):e73094.

74. Witt SN. Lipid disequilibrium in biological membranes, a possible pathway to neurodegeneration. Commun Integr Biol 2014;7(6):e993266.

75. Norris SE, Friedrich MG, Mitchell TW, Truscott RJ, Else PL. Human prefrontal cortex phospholipids containing docosahexaenoic acid increase during normal adult aging, whereas those containing arachidonic acid decrease. Neurobiol Aging 2015;36(4):1659-1669.

76. von Bernhardi R, Eugenin-von Bernhardi L, Eugenin J. Microglial cell dysregulation in brain aging and neurodegeneration. Front Aging Neurosci 2015;7:124.

77. Drzezga A, Grimmer T, Henriksen G, et al. Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease. Neurology 2009;72(17):1487-1494.

78. Blazquez L, Otaegui D, Saenz A, et al. Apolipoprotein E epsilon4 allele in familial and sporadic Parkinson's disease. Neurosci Lett 2006;406(3):235-239.

79. Feldman B, Chapman J, Korczyn AD. Apolipoprotein epsilon4 advances appearance of psychosis in patients with Parkinson's disease. Acta Neurol Scand 2006;113(1):14-17.

80. Pankratz N, Byder L, Halter C, et al. Presence of an APOE4 allele results in significantly earlier onset of Parkinson's disease and a higher risk with dementia. Mov Disord 2006;21(1):45-49.

81. Papapetropoulos S, Farrer MJ, Stone JT, et al. Phenotypic associations of tau and ApoE in Parkinson's disease. Neurosci Lett 2007;414(2):141-144.

82. Monsell SE, Besser LM, Heller KB, Checkoway H, Litvan I, Kukull WA. Clinical and pathologic presentation in Parkinson's disease by apolipoprotein e4 allele status. Parkinsonism Relat Disord 2014;20(5):503-507.

83. Mata IF, Leverenz JB, Weintraub D, et al. APOE, MAPT, and SNCA genes and cognitive performance in Parkinson disease. JAMA Neurol 2014;71(11):1405-1412.

84. Koller WC, Glatt SL, Hubble JP, et al. Apolipoprotein E genotypes in Parkinson's disease with and without dementia. Ann Neurol 1995;37(2):242-245.

85. Parsian A, Racette B, Goldsmith LJ, Perlmutter JS. Parkinson's disease and apolipoprotein E: possible association with dementia but not age at onset. Genomics 2002;79(3):458-461.

86. Camicioli R, Rajput A, Rajput M, et al. Apolipoprotein E epsilon4 and catechol-O-methyltransferase alleles in autopsy-proven Parkinson's disease: relationship to dementia and hallucinations. Mov Disord 2005;20(8):989-994.

87. Jasinska-Myga B, Opala G, Goetz CG, et al. Apolipoprotein E gene polymorphism, total plasma cholesterol level, and Parkinson disease dementia. Arch Neurol 2007;64(2):261-265.

88. Ezquerra M, Campdelacreu J, Gaig C, et al. Lack of association of APOE and tau polymorphisms with dementia in Parkinson's disease. Neurosci Lett 2008;448(1):20-23.

89. Kurz MW, Dekomien G, Nilsen OB, Larsen JP, Aarsland D, Alves G. APOE alleles in Parkinson disease and their relationship to cognitive decline: a population-based, longitudinal study. J Geriatr Psychiatry Neurol 2009;22(3):166-170.

90. Troster AI, Fields JA, Paolo AM, Koller WC. Absence of the apolipoprotein E epsilon4 allele is associated with working memory impairment in Parkinson's disease. J Neurol Sci 2006;248(1-2):62-67.

91. Williams-Gray CH, Goris A, Saiki M, et al. Apolipoprotein E genotype as a risk factor for susceptibility to and dementia in Parkinson's disease. J Neurol 2009;256(3):493-498.

92. Morley JF, Xie SX, Hurtig HI, et al. Genetic influences on cognitive decline in Parkinson's disease. Mov Disord 2012;27(4):512-518.

93. Lane R, He Y, Morris C, Leverenz JB, Emre M, Ballard C. BuChE-K and APOE epsilon4 allele frequencies in Lewy body dementias, and influence of genotype and hyperhomocysteinemia on cognitive decline. Mov Disord 2009;24(3):392-400.

94. de Lau LM, Schipper CM, Hofman A, Koudstaal PJ, Breteler MM. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. Arch Neurol 2005;62(8):1265-1269.

95. Harhangi BS, de Rijk MC, van Duijn CM, Van Broeckhoven C, Hofman A, Breteler MM. APOE and the risk of PD with or without dementia in a population-based study. Neurology 2000;54(6):1272-1276.

96. Seto-Salvia N, Clarimon J, Pagonabarraga J, et al. Dementia risk in Parkinson disease: disentangling the role of MAPT haplotypes. Arch Neurol 2011;68(3):359-364.

97. 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(Pt 11):2958-2969.

98. Goris A, Williams-Gray CH, Clark GR, et al. Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. Ann Neurol 2007;62(2):145-153.

99. Winder-Rhodes SE, Hampshire A, Rowe JB, et al. Association between MAPT haplotype and memory function in patients with Parkinson's disease and healthy aging individuals. Neurobiol Aging 2015;36(3):1519-1528.

100. Nishioka K, Ross OA, Ishii K, et al. Expanding the clinical phenotype of SNCA duplication carriers. Mov Disord 2009;24(12):1811-1819.

101. Farrer M, Kachergus J, Forno L, et al. Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. Ann Neurol 2004;55(2):174-179.

102. Somme JH, Gomez-Esteban JC, Molano A, Tijero B, Lezcano E, Zarranz JJ. Initial neuropsychological impairments in patients with the E46K mutation of the alpha-synuclein gene (PARK 1). J Neurol Sci 2011;310(1-2):86-89.

103. Tokutake T, Ishikawa A, Yoshimura N, et al. Clinical and neuroimaging features of patient with early-onset Parkinson's disease with dementia carrying SNCA p.G51D mutation. Parkinsonism Relat Disord 2014;20(2):262-264.

104. De Marco EV, Tarantino P, Rocca FE, et al. Alpha-synuclein promoter haplotypes and dementia in Parkinson's disease. Am J Med Genet B Neuropsychiatr Genet 2008;147(3):403-407.

105. Seto-Salvia N, Pagonabarraga J, Houlden H, et al. Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. Mov Disord 2012;27(3):393-399.

106. Alcalay RN, Caccappolo E, Mejia-Santana H, et al. Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. Neurology 2012;78(18):1434-1440.

107. Alcalay RN, Mejia-Santana H, Tang MX, et al. Self-report of cognitive impairment and mini-mental state examination performance in PRKN, LRRK2, and GBA carriers with early onset Parkinson's disease. J Clin Exp Neuropsychol 2010;32(7):775-779.

108. Brockmann K, Srulijes K, Pflederer S, et al. GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Mov Disord 2015;30(3):407-411.

109. Winder-Rhodes SE, Evans JR, Ban M, et al. Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. Brain 2013;136(Pt 2):392-399.

110. Beavan MS, Schapira AH. Glucocerebrosidase mutations and the pathogenesis of Parkinson disease. Ann Med 2013;45(8):511-521.

111. Williams-Gray CH, Hampshire A, Robbins TW, Owen AM, Barker RA. Catechol O-methyltransferase Val158Met genotype influences frontoparietal activity during planning in patients with Parkinson's disease. J Neurosci 2007;27(18):4832-4838.

112. Foltynie T, Goldberg TE, Lewis SG, et al. Planning ability in Parkinson's disease is influenced by the COMT val158met polymorphism. Mov Disord 2004;19(8):885-891.

113. Williams-Gray CH, Hampshire A, Barker RA, Owen AM. Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. Brain 2008;131(Pt 2):397-408.

114. Hoogland J, de Bie RM, Williams-Gray CH, Muslimovic D, Schmand B, Post B. Catechol-O-methyltransferase val158met and cognitive function in Parkinson's disease. Mov Disord 2010;25(15):2550-2554.

115. Nombela C, Rowe JB, Winder-Rhodes SE, et al. Genetic impact on cognition and brain function in newly diagnosed Parkinson's disease: ICICLE-PD study. Brain 2014;137(Pt 10):2743-2758.

116. Hudson G, Stutt A, Eccles M, et al. Genetic variation of CHRNA4 does not modulate attention in Parkinson's disease. Neurosci Lett 2010;479(2):123-125.

117. Nie K, Zhang Y, Gan R, et al. Polymorphisms in immune/inflammatory cytokine genes are related to Parkinson's disease with cognitive impairment in the Han Chinese population. Neurosci Lett 2013;541:111-115.

118. Bialecka M, Kurzawski M, Roszmann A, et al. BDNF G196A (Val66Met) polymorphism associated with cognitive impairment in Parkinson's disease. Neurosci Lett 2014;561:86-90.

119. Guerini FR, Beghi E, Riboldazzi G, et al. BDNF Val66Met polymorphism is associated with cognitive impairment in Italian patients with Parkinson's disease. Eur J Neurol 2009;16(11):1240-1245.

120. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT. Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 2004;127(Pt 4):791-800.

121. Pagonabarraga J, Corcuera-Solano I, Vives-Gilabert Y, et al. Pattern of regional cortical thinning associated with cognitive deterioration in Parkinson's disease. PLoS One 2013;8(1):e54980.

122. Tam CW, Burton EJ, McKeith IG, Burn DJ, O'Brien JT. Temporal lobe atrophy on MRI in Parkinson disease with dementia: a comparison with Alzheimer disease and dementia with Lewy bodies. Neurology 2005;64(5):861-865.

123. Choi SH, Jung TM, Lee JE, Lee SK, Sohn YH, Lee PH. Volumetric analysis of the substantia innominata in patients with Parkinson's disease according to cognitive status. Neurobiol Aging 2012;33(7):1265-1272.

124. Borroni B, Premi E, Formenti A, et al. Structural and functional imaging study in dementia with Lewy bodies and Parkinson's disease dementia. Parkinsonism Relat Disord 2015.

125. Biundo R, Calabrese M, Weis L, et al. Anatomical correlates of cognitive functions in early Parkinson's disease patients. PLoS One 2013;8(5):e64222.

126. Jokinen P, Bruck A, Aalto S, Forsback S, Parkkola R, Rinne JO. Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy. Parkinsonism Relat Disord 2009;15(2):88-93.

127. Mak E, Zhou J, Tan LC, Au WL, Sitoh YY, Kandiah N. Cognitive deficits in mild Parkinson's disease are associated with distinct areas of grey matter atrophy. J Neurol Neurosurg Psychiatry 2014;85(5):576-580.

128. Noh SW, Han YH, Mun CW, et al. Analysis among cognitive profiles and gray matter volume in newly diagnosed Parkinson's disease with mild cognitive impairment. J Neurol Sci 2014;347(1-2):210-213.

129. Apostolova LG, Beyer M, Green AE, et al. Hippocampal, caudate, and ventricular changes in Parkinson's disease with and without dementia. Mov Disord 2010;25(6):687-695.

130. Compta Y, Ibarretxe-Bilbao N, Pereira JB, et al. Grey matter volume correlates of cerebrospinal markers of Alzheimer-pathology in Parkinson's disease and related dementia. Parkinsonism Relat Disord 2012;18(8):941-947.

131. Kenny ER, Burton EJ, O'Brien JT. A volumetric magnetic resonance imaging study of entorhinal cortex volume in dementia with lewy bodies. A comparison with Alzheimer's disease and Parkinson's disease with and without dementia. Dement Geriatr Cogn Disord 2008;26(3):218-225.

132. Junque C, Ramirez-Ruiz B, Tolosa E, et al. Amygdalar and hippocampal MRI volumetric reductions in Parkinson's disease with dementia. Mov Disord 2005;20(5):540-544.

133. Camicioli R, Moore MM, Kinney A, Corbridge E, Glassberg K, Kaye JA. Parkinson's disease is associated with hippocampal atrophy. Mov Disord 2003;18(7):784-790.

134. Nagano-Saito A, Washimi Y, Arahata Y, et al. Cerebral atrophy and its relation to cognitive impairment in Parkinson disease. Neurology 2005;64(2):224-229.

135. Summerfield C, Junque C, Tolosa E, et al. Structural brain changes in Parkinson disease with dementia: a voxel-based morphometry study. Arch Neurol 2005;62(2):281-285.

136. Beyer MK, Janvin CC, Larsen JP, Aarsland D. A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. J Neurol Neurosurg Psychiatry 2007;78(3):254-259.

137. Song SK, Lee JE, Park HJ, Sohn YH, Lee JD, Lee PH. The pattern of cortical atrophy in patients with Parkinson's disease according to cognitive status. Mov Disord 2011;26(2):289-296.

138. Melzer TR, Watts R, MacAskill MR, et al. Grey matter atrophy in cognitively impaired Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;83(2):188-194.

139. Goldman JG, Stebbins GT, Bernard B, Stoub TR, Goetz CG, deToledo-Morrell L. Entorhinal cortex atrophy differentiates Parkinson's disease patients with and without dementia. Mov Disord 2012;27(6):727-734.

140. Ibarretxe-Bilbao N, Ramirez-Ruiz B, Tolosa E, et al. Hippocampal head atrophy predominance in Parkinson's disease with hallucinations and with dementia. J Neurol 2008;255(9):1324-1331.

141. Nishio Y, Hirayama K, Takeda A, et al. Corticolimbic gray matter loss in Parkinson's disease without dementia. Eur J Neurol 2010;17(8):1090-1097.

142. Weintraub D, Doshi J, Koka D, et al. Neurodegeneration across stages of cognitive decline in Parkinson disease. Arch Neurol 2011;68(12):1562-1568.

143. Hwang KS, Beyer MK, Green AE, et al. Mapping cortical atrophy in Parkinson's disease patients with dementia. J Parkinsons Dis 2013;3(1):69-76.

144. Lee SH, Kim SS, Tae WS, Lee SY, Lee KU, Jhoo J. Brain volumetry in Parkinson's disease with and without dementia: where are the differences? Acta Radiol 2013;54(5):581-586.

145. Zarei M, Ibarretxe-Bilbao N, Compta Y, et al. Cortical thinning is associated with disease stages and dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 2013;84(8):875-881.

146. Pereira JB, Svenningsson P, Weintraub D, et al. Initial cognitive decline is associated with cortical thinning in early Parkinson disease. Neurology 2014;82(22):2017-2025.

147. Kim HJ, Lee JE, Shin SJ, Sohn YH, Lee PH. Analysis of the substantia innominata volume in patients with Parkinson's disease with dementia, dementia with lewy bodies, and Alzheimer's disease. J Mov Disord 2011;4(2):68-72.

148. Hanganu A, Bedetti C, Jubault T, et al. Mild cognitive impairment in patients with Parkinson's disease is associated with increased cortical degeneration. Mov Disord 2013;28(10):1360-1369.

149. Danti S, Toschi N, Diciotti S, et al. Cortical thickness in de novo patients with Parkinson disease and mild cognitive impairment with consideration of clinical phenotype and motor laterality. Eur J Neurol 2015.

150. Segura B, Baggio HC, Marti MJ, et al. Cortical thinning associated with mild cognitive impairment in Parkinson's disease. Mov Disord 2014;29(12):1495-1503.

151. Lee JE, Park B, Song SK, Sohn YH, Park HJ, Lee PH. A comparison of gray and white matter density in patients with Parkinson's disease dementia and dementia with Lewy bodies using voxel-based morphometry. Mov Disord 2010;25(1):28-34.

152. Mak E, Su L, Williams GB, et al. Baseline and longitudinal grey matter changes in newly diagnosed Parkinson's disease: ICICLE-PD study. Brain 2015.

153. Hattori T, Orimo S, Aoki S, et al. Cognitive status correlates with white matter alteration in Parkinson's disease. Hum Brain Mapp 2012;33(3):727-739.

154. Laakso MP, Partanen K, Riekkinen P, et al. Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: An MRI study. Neurology 1996;46(3):678-681.

155. Bruck 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(10):1467-1469.

156. Oikawa H, Sasaki M, Ehara S, Abe T. Substantia innominata: MR findings in Parkinson's disease. Neuroradiology 2004;46(10):817-821.

157. Filoteo JV, Reed JD, Litvan I, Harrington DL. Volumetric correlates of cognitive functioning in nondemented patients with Parkinson's disease. Mov Disord 2014;29(3):360-367.

158. 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(3):187-195.

159. Ibarretxe-Bilbao N, Junque C, Tolosa E, et al. Neuroanatomical correlates of impaired decision-making and facial emotion recognition in early Parkinson's disease. Eur J Neurosci 2009;30(6):1162-1171.

160. Duncan GW, Firbank MJ, Yarnall AJ, et al. Gray and white matter imaging: A biomarker for cognitive impairment in early Parkinson's disease? Mov Disord 2015.

161. Koshimori Y, Segura B, Christopher L, et al. Imaging changes associated with cognitive abnormalities in Parkinson's disease. Brain Struct Funct 2014.

162. Garcia-Diaz AI, Segura B, Baggio HC, et al. Structural MRI correlates of the MMSE and pentagon copying test in Parkinson's disease. Parkinsonism Relat Disord 2014;20(12):1405-1410.

163. Lee JE, Cho KH, Song SK, et al. Exploratory analysis of neuropsychological and neuroanatomical correlates of progressive mild cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry 2014;85(1):7-16.

164. Kandiah N, Zainal NH, Narasimhalu K, et al. Hippocampal volume and white matter disease in the prediction of dementia in Parkinson's disease. Parkinsonism Relat Disord 2014;20(11):1203-1208.

165. Morales DA, Vives-Gilabert Y, Gomez-Anson B, et al. Predicting dementia development in Parkinson's disease using Bayesian network classifiers. Psychiatry Res 2013;213(2):92-98.

166. Melzer TR, Watts R, MacAskill MR, et al. White matter microstructure deteriorates across cognitive stages in Parkinson disease. Neurology 2013;80(20):1841-1849.

167. Kamagata K, Motoi Y, Abe O, et al. White matter alteration of the cingulum in Parkinson disease with and without dementia: evaluation by diffusion tensor tract-specific analysis. AJNR Am J Neuroradiol 2012;33(5):890-895.

168. Kamagata K, Motoi Y, Tomiyama H, et al. Relationship between cognitive impairment and white-matter alteration in Parkinson's disease with dementia: tract-based spatial statistics and tract-specific analysis. Eur Radiol 2013;23(7):1946-1955.

169. Deng B, Zhang Y, Wang L, et al. Diffusion tensor imaging reveals white matter changes associated with cognitive status in patients with Parkinson's disease. Am J Alzheimers Dis Other Demen 2013;28(2):154-164.

170. Matsui H, Nishinaka K, Oda M, Niikawa H, Kubori T, Udaka F. Dementia in Parkinson's disease: diffusion tensor imaging. Acta Neurol Scand 2007;116(3):177-181.

171. Agosta F, Canu E, Stefanova E, et al. Mild cognitive impairment in Parkinson's disease is associated with a distributed pattern of brain white matter damage. Hum Brain Mapp 2014;35(5):1921-1929.

172. Chen B, Fan GG, Liu H, Wang S. Changes in anatomical and functional connectivity of Parkinson's disease patients according to cognitive status. Eur J Radiol 2015;84(7):1318-1324.

173. Agosta F, Canu E, Stojkovic T, et al. The topography of brain damage at different stages of Parkinson's disease. Hum Brain Mapp 2012.

174. Zheng Z, Shemmassian S, Wijekoon C, Kim W, Bookheimer SY, Pouratian N. DTI correlates of distinct cognitive impairments in Parkinson's disease. Hum Brain Mapp 2013.

175. Theilmann RJ, Reed JD, Song DD, et al. White-matter changes correlate with cognitive functioning in Parkinson's disease. Front Neurol 2013;4:37.

176. Ekman U, Eriksson J, Forsgren L, Mo SJ, Riklund K, Nyberg L. Functional brain activity and presynaptic dopamine uptake in patients with Parkinson's disease and

mild cognitive impairment: a cross-sectional study. Lancet Neurol 2012;11(8):679-687.

177. Nagano-Saito A, Habak C, Mejia-Constain B, et al. Effect of mild cognitive impairment on the patterns of neural activity in early Parkinson's disease. Neurobiol Aging 2014;35(1):223-231.

178. Ekman U, Eriksson J, Forsgren L, et al. Longitudinal changes in task-evoked brain responses in Parkinson's disease patients with and without mild cognitive impairment. Front Neurosci 2014;8:207.

179. Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. J Neurosci 2003;23(15):6351-6356.

180. Williams-Gray CH, Mason SL, Evans JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry 2013;84(11):1258-1264.

181. Pagonabarraga J, Kulisevsky J, Llebaria G, Garcia-Sanchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. Mov Disord 2008;23(7):998-1005.

182. Seibert TM, Murphy EA, Kaestner EJ, Brewer JB. Interregional correlations in Parkinson disease and Parkinson-related dementia with resting functional MR imaging. Radiology 2012;263(1):226-234.

183. Rektorova I, Krajcovicova L, Marecek R, Mikl M. Default mode network and extrastriate visual resting state network in patients with Parkinson's disease dementia. Neurodegener Dis 2012;10(1-4):232-237.

184. Baggio HC, Sala-Llonch R, Segura B, et al. Functional brain networks and cognitive deficits in Parkinson's disease. Hum Brain Mapp 2014.

185. Pereira JB, Aarsland D, Ginestet CE, et al. Aberrant cerebral network topology and mild cognitive impairment in early Parkinson's disease. Hum Brain Mapp 2015.

186. Amboni M, Tessitore A, Esposito F, et al. Resting-state functional connectivity associated with mild cognitive impairment in Parkinson's disease. J Neurol 2015;262(2):425-434.

187. Olde Dubbelink KT, Schoonheim MM, Deijen JB, Twisk JW, Barkhof F, Berendse HW. Functional connectivity and cognitive decline over 3 years in Parkinson disease. Neurology 2014;83(22):2046-2053.

188. Rektorova I, Krajcovicova L, Marecek R, Novakova M, Mikl M. Default mode network connectivity patterns associated with visual processing at different stages of Parkinson's disease. J Alzheimers Dis 2014;42 Suppl 3:S217-228.

189. Nie K, Zhang Y, Huang B, et al. Marked N-acetylaspartate and choline metabolite changes in Parkinson's disease patients with mild cognitive impairment. Parkinsonism Relat Disord 2013;19(3):329-334.

190. Summerfield C, Gomez-Anson B, Tolosa E, et al. Dementia in Parkinson disease: a proton magnetic resonance spectroscopy study. Arch Neurol 2002;59(9):1415-1420.

191. Griffith HR, den Hollander JA, Okonkwo OC, O'Brien T, Watts RL, Marson DC. Brain N-acetylaspartate is reduced in Parkinson disease with dementia. Alzheimer Dis Assoc Disord 2008;22(1):54-60.

192. Pagonabarraga J, Gomez-Anson B, Rotger R, et al. Spectroscopic changes associated with mild cognitive impairment and dementia in Parkinson's disease. Dement Geriatr Cogn Disord 2012;34(5-6):312-318.

193. Camicioli RM, Korzan JR, Foster SL, et al. Posterior cingulate metabolic changes occur in Parkinson's disease patients without dementia. Neurosci Lett 2004;354(3):177-180.

194. Lewis SJ, Shine JM, Duffy S, Halliday G, Naismith SL. Anterior cingulate integrity: executive and neuropsychiatric features in Parkinson's disease. Mov Disord 2012;27(10):1262-1267.

195. Hu MT, Taylor-Robinson SD, Chaudhuri KR, et al. Cortical dysfunction in non-demented Parkinson's disease patients: a combined (31)P-MRS and (18)FDG-PET study. Brain 2000;123 (Pt 2):340-352.

196. Ito K, Nagano-Saito A, Kato T, et al. Striatal and extrastriatal dysfunction in Parkinson's disease with dementia: a 6-[18F]fluoro-L-dopa PET study. Brain 2002;125(Pt 6):1358-1365.

197. 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):565-575.

198. Chou KL, Lenhart A, Koeppe RA, Bohnen NI. Abnormal MoCA and normal range MMSE scores in Parkinson disease without dementia: cognitive and neurochemical correlates. Parkinsonism Relat Disord 2014;20(10):1076-1080.

199. Christopher L, Duff-Canning S, Koshimori Y, et al. Salience network and parahippocampal dopamine dysfunction in memory-impaired Parkinson disease. Ann Neurol 2015;77(2):269-280.

200. van Beilen M, Leenders KL. Putamen FDOPA uptake and its relationship tot cognitive functioning in PD. J Neurol Sci 2006;248(1-2):68-71.

201. Nobili F, Campus C, Arnaldi D, et al. Cognitive-nigrostriatal relationships in de novo, drug-naive Parkinson's disease patients: a [I-123]FP-CIT SPECT study. Mov Disord 2010;25(1):35-43.

202. Siepel FJ, Bronnick KS, Booij J, et al. Cognitive executive impairment and dopaminergic deficits in de novo Parkinson's disease. Mov Disord 2014;29(14):1802-1808.

203. Pellecchia MT, Picillo M, Santangelo G, et al. Cognitive performances and DAT imaging in early Parkinson's disease with mild cognitive impairment: a preliminary study. Acta Neurol Scand 2015;131(5):275-281.

204. Bruck A, Portin R, Lindell A, et al. Positron emission tomography shows that impaired frontal lobe functioning in Parkinson's disease is related to dopaminergic hypofunction in the caudate nucleus. Neurosci Lett 2001;311(2):81-84.

205. Rektorova I, Srovnalova H, Kubikova R, Prasek J. Striatal dopamine transporter imaging correlates with depressive symptoms and tower of London task performance in Parkinson's disease. Mov Disord 2008;23(11):1580-1587.

206. Lebedev AV, Westman E, Simmons A, et al. Large-scale resting state network correlates of cognitive impairment in Parkinson's disease and related dopaminergic deficits. Front Syst Neurosci 2014;8:45.

207. Colloby SJ, Williams ED, Burn DJ, Lloyd JJ, McKeith IG, O'Brien JT. Progression of dopaminergic degeneration in dementia with Lewy bodies and Parkinson's disease with and without dementia assessed using 123I-FP-CIT SPECT. Eur J Nucl Med Mol Imaging 2005;32(10):1176-1185.

208. Broussolle E, Dentresangle C, Landais P, et al. The relation of putamen and caudate nucleus 18F-Dopa uptake to motor and cognitive performances in Parkinson's disease. J Neurol Sci 1999;166(2):141-151.

209. Song IU, Kim YD, Cho HJ, Chung SW, Chung YA. An FP-CIT PET comparison of the differences in dopaminergic neuronal loss between idiopathic Parkinson disease with dementia and without dementia. Alzheimer Dis Assoc Disord 2013;27(1):51-55.

210. Liu AK, Chang RC, Pearce RK, Gentleman SM. Nucleus basalis of Meynert revisited: anatomy, history and differential involvement in Alzheimer's and Parkinson's disease. Acta Neuropathol 2015;129(4):527-540.

211. Poewe W, Wolters E, Emre M, et al. Long-term benefits of rivastigmine in dementia associated with Parkinson's disease: an active treatment extension study. Mov Disord 2006;21(4):456-461.

212. Klein JC, Eggers C, Kalbe E, et al. Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. Neurology 2010;74(11):885-892.

213. Shimada H, Hirano S, Shinotoh H, et al. Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET. Neurology 2009;73(4):273-278.

214. Kuhl DE, Minoshima S, Fessler JA, et al. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. Ann Neurol 1996;40(3):399-410.

215. Hilker R, Thomas AV, Klein JC, et al. Dementia in Parkinson disease: functional imaging of cholinergic and dopaminergic pathways. Neurology 2005;65(11):1716-1722.

216. Bohnen NI1, Kaufer DI, Ivanco LS, Lopresti B, Koeppe RA, Davis JG, Mathis CA, Moore RY, DeKosky ST. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol. 2003 Dec;60(12):1745-8.

217. Bohnen NI, Kaufer DI, Hendrickson R, et al. Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia. J Neurol 2006;253(2):242-247.

218. Meyer PM, Strecker K, Kendziorra K, et al. Reduced alpha4beta2*-nicotinic acetylcholine receptor binding and its relationship to mild cognitive and depressive symptoms in Parkinson disease. Arch Gen Psychiatry 2009;66(8):866-877.

219. Bohnen NI, Muller ML, Kotagal V, et al. Heterogeneity of cholinergic denervation in Parkinson's disease without dementia. J Cereb Blood Flow Metab 2012;32(8):1609-1617.

220. Bohnen NI, Albin RL, Muller ML, et al. Frequency of cholinergic and caudate nucleus dopaminergic deficits across the predemented cognitive spectrum of Parkinson disease and evidence of interaction effects. JAMA Neurol 2015;72(2):194-200.

221. Lorenz R, Samnick S, Dillmann U, et al. Nicotinic alpha4beta2 acetylcholine receptors and cognitive function in Parkinson's disease. Acta Neurol Scand 2014;130(3):164-171.

222. Edison P, Rowe CC, Rinne JO, et al. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. J Neurol Neurosurg Psychiatry 2008;79(12):1331-1338.

223. Shimada H, Shinotoh H, Hirano S, et al. beta-Amyloid in Lewy body disease is related to Alzheimer's disease-like atrophy. Mov Disord 2013;28(2):169-175.

224. Petrou M, Bohnen NI, Muller ML, Koeppe RA, Albin RL, Frey KA. Abeta-amyloid deposition in patients with Parkinson disease at risk for development of dementia. Neurology 2012;79(11):1161-1167.

225. Maetzler W, Reimold M, Liepelt I, et al. [11C]PIB binding in Parkinson's disease dementia. Neuroimage 2008;39(3):1027-1033.

226. Burack MA, Hartlein J, Flores HP, Taylor-Reinwald L, Perlmutter JS, Cairns NJ. In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia. Neurology 2010;74(1):77-84.

227. Campbell MC, Markham J, Flores H, et al. Principal component analysis of PiB distribution in Parkinson and Alzheimer diseases. Neurology 2013;81(6):520-527.

228. Gomperts SN, Locascio JJ, Marquie M, et al. Brain amyloid and cognition in Lewy body diseases. Mov Disord 2012;27(8):965-973.

229. Foster ER, Campbell MC, Burack MA, et al. Amyloid imaging of Lewy body-associated disorders. Mov Disord 2010;25(15):2516-2523.

230. Gomperts SN, Locascio JJ, Rentz D, et al. Amyloid is linked to cognitive decline in patients with Parkinson disease without dementia. Neurology 2013;80(1):85-91.

231. Lucero C, Campbell MC, Flores H, Maiti B, Perlmutter JS, Foster ER. Cognitive reserve and beta-amyloid pathology in Parkinson disease. Parkinsonism Relat Disord 2015;21(8):899-904.

232. Irwin DJ, White MT, Toledo JB, et al. Neuropathologic substrates of Parkinson disease dementia. Ann Neurol 2012;72(4):587-598.

233. Petrou M, Dwamena BA, Foerster BR, et al. Amyloid deposition in Parkinson's disease and cognitive impairment: A systematic review. Mov Disord 2015;30(7):928-935.

234. Osaki Y, Morita Y, Fukumoto M, Akagi N, Yoshida S, Doi Y. Three-dimensional stereotactic surface projection SPECT analysis in Parkinson's disease with and without dementia. Mov Disord 2005;20(8):999-1005.

235. Matsui H, Udaka F, Miyoshi T, et al. N-isopropyl-p- 123I iodoamphetamine single photon emission computed tomography study of Parkinson's disease with dementia. Intern Med 2005;44(10):1046-1050.

236. Derejko M, Slawek J, Wieczorek D, Brockhuis B, Dubaniewicz M, Lass P. Regional cerebral blood flow in Parkinson's disease as an indicator of cognitive impairment. Nucl Med Commun 2006;27(12):945-951.

237. Wallin A, Ekberg S, Lind K, Milos V, Granerus AK, Granerus G. Posterior cortical brain dysfunction in cognitively impaired patients with Parkinson's disease--a rCBF scintigraphy study. Acta Neurol Scand 2007;116(6):347-354.

238. Wang SJ, Liu RS, Liu HC, et al. Technetium-99m hexamethylpropylene amine oxime single photon emission tomography of the brain in early Parkinson's disease: correlation with dementia and lateralization. Eur J Nucl Med 1993;20(4):339-344.

239. Liu RS, Lin KN, Wang SJ, et al. Cognition and 99Tcm-HMPAO SPECT in Parkinson's disease. Nucl Med Commun 1992;13(10):744-748.

240. Spampinato U, Habert MO, Mas JL, et al. (99mTc)-HM-PAO SPECT and cognitive impairment in Parkinson's disease: a comparison with dementia of the Alzheimer type. J Neurol Neurosurg Psychiatry 1991;54(9):787-792.

241. Kawabata K, Tachibana H, Sugita M. Cerebral blood flow and dementia in Parkinson's disease. J Geriatr Psychiatry Neurol 1991;4(4):194-203.

242. Kasama S, Tachibana H, Kawabata K, Yoshikawa H. Cerebral blood flow in Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease according to three-dimensional stereotactic surface projection imaging. Dement Geriatr Cogn Disord 2005;19(5-6):266-275.

243. Hattori N, Yabe I, Hirata K, et al. Brain regions associated with cognitive impairment in patients with Parkinson disease: quantitative analysis of cerebral blood flow using 123I iodoamphetamine SPECT. Clin Nucl Med 2013;38(5):315-320.

244. Nobili F, Abbruzzese G, Morbelli S, et al. Amnestic mild cognitive impairment in Parkinson's disease: a brain perfusion SPECT study. Mov Disord 2009;24(3):414-421.

245. Song IU, Chung YA, Chung SW, Jeong J. Early diagnosis of Alzheimer's disease and Parkinson's disease associated with dementia using cerebral perfusion SPECT. Dement Geriatr Cogn Disord 2014;37(5-6):276-285.

246. Matsui H, Nishinaka K, Oda M, et al. Heterogeneous factors in dementia with Parkinson's disease: IMP-SPECT study. Parkinsonism Relat Disord 2007;13(3):174-181.

247. Sawada H, Udaka F, Kameyama M, et al. SPECT findings in Parkinson's disease associated with dementia. J Neurol Neurosurg Psychiatry 1992;55(10):960-963.

248. Antonini A, De Notaris R, Benti R, De Gaspari D, Pezzoli G. Perfusion ECD/SPECT in the characterization of cognitive deficits in Parkinson's disease. Neurol Sci 2001;22(1):45-46.

249. Mito Y, Yoshida K, Yabe I, et al. Brain 3D-SSP SPECT analysis in dementia with Lewy bodies, Parkinson's disease with and without dementia, and Alzheimer's disease. Clin Neurol Neurosurg 2005;107(5):396-403.

250. Edison P, Ahmed I, Fan Z, et al. Microglia, amyloid, and glucose metabolism in Parkinson's disease with and without dementia. Neuropsychopharmacology 2013;38(6):938-949.

251. Garcia-Garcia D, Clavero P, Gasca Salas C, et al. Posterior parietooccipital hypometabolism may differentiate mild cognitive impairment from dementia in Parkinson's disease. Eur J Nucl Med Mol Imaging 2012;39(11):1767-1777.

252. Gonzalez-Redondo R, Garcia-Garcia D, Clavero P, et al. Grey matter hypometabolism and atrophy in Parkinson's disease with cognitive impairment: a two-step process. Brain 2014;137(Pt 8):2356-2367.

253. Jokinen P, Scheinin N, Aalto S, et al. [(11)C]PIB-, [(18)F]FDG-PET and MRI imaging in patients with Parkinson's disease with and without dementia. Parkinsonism Relat Disord 2010;16(10):666-670.

254. Yong SW, Yoon JK, An YS, Lee PH. A comparison of cerebral glucose metabolism in Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies. Eur J Neurol 2007;14(12):1357-1362.

255. Huang C, Mattis P, Perrine K, Brown N, Dhawan V, Eidelberg D. Metabolic abnormalities associated with mild cognitive impairment in Parkinson disease. Neurology 2008;70(16 Pt 2):1470-1477.

256. Hosokai Y, Nishio Y, Hirayama K, et al. Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment. Mov Disord 2009;24(6):854-862.

257. Lyoo CH, Jeong Y, Ryu YH, Rinne JO, Lee MS. Cerebral glucose metabolism of Parkinson's disease patients with mild cognitive impairment. Eur Neurol 2010;64(2):65-73.

258. Pappata S, Santangelo G, Aarsland D, et al. Mild cognitive impairment in drug-naive patients with PD is associated with cerebral hypometabolism. Neurology 2011;77(14):1357-1362.

259. Bohnen NI, Koeppe RA, Minoshima S, et al. Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study. J Nucl Med 2011;52(6):848-855.

260. Shoji Y, Nishio Y, Baba T, et al. Neural substrates of cognitive subtypes in Parkinson's disease: a 3-year longitudinal study. PLoS One 2014;9(10):e110547.

261. Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D. Metabolic brain networks associated with cognitive function in Parkinson's disease. Neuroimage 2007;34(2):714-723.

262. Huang C, Ravdin LD, Nirenberg MJ, et al. Neuroimaging markers of motor and nonmotor features of Parkinson's disease: an 18f fluorodeoxyglucose positron emission computed tomography study. Dement Geriatr Cogn Disord 2013;35(3-4):183-196.

263. Nagano-Saito A, Kato T, Arahata Y, et al. Cognitive- and motor-related regions in Parkinson's disease: FDOPA and FDG PET studies. Neuroimage 2004;22(2):553-561.

264. Lozza C, Baron JC, Eidelberg D, Mentis MJ, Carbon M, Marie RM. Executive processes in Parkinson's disease: FDG-PET and network analysis. Hum Brain Mapp 2004;22(3):236-245.

265. Abe Y, Kachi T, Kato T, et al. Occipital hypoperfusion in Parkinson's disease without dementia: correlation to impaired cortical visual processing. J Neurol Neurosurg Psychiatry 2003;74(4):419-422.

266. Paschali A, Messinis L, Lyros E, et al. Neuropsychological functions and rCBF SPECT in Parkinson's disease patients considered candidates for deep brain stimulation. Eur J Nucl Med Mol Imaging 2009;36(11):1851-1858.

267. Kramberger MG, Stukovnik V, Cus A, et al. Parkinson's disease dementia: clinical correlates of brain spect perfusion and treatment. Psychiatr Danub 2010;22(3):446-449.

268. Neufeld MY, Inzelberg R, Korczyn AD. EEG in demented and non-demented parkinsonian patients. Acta Neurol Scand 1988;78(1):1-5.

269. Neufeld MY, Blumen S, Aitkin I, Parmet Y, Korczyn AD. EEG frequency analysis in demented and nondemented parkinsonian patients. Dementia 1994;5(1):23-28.

270. Bonanni L, Thomas A, Tiraboschi P, Perfetti B, Varanese S, Onofrj M. EEG comparisons in early Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease with dementia patients with a 2-year follow-up. Brain 2008;131(Pt 3):690-705.

271. Serizawa K, Kamei S, Morita A, et al. Comparison of quantitative EEGs between Parkinson disease and age-adjusted normal controls. J Clin Neurophysiol 2008;25(6):361-366.

272. Soikkeli R, Partanen J, Soininen H, Paakkonen A, Riekkinen P, Sr. Slowing of EEG in Parkinson's disease. Electroencephalogr Clin Neurophysiol 1991;79(3):159-165.

273. Fonseca LC, Tedrus GM, Carvas PN, Machado EC. Comparison of quantitative EEG between patients with Alzheimer's disease and those with Parkinson's disease dementia. Clin Neurophysiol 2013.

274. Domitrz I, Friedman A. Electroencephalography of demented and non-demented Parkinson's disease patients. Parkinsonism Relat Disord 1999;5(1-2):37-41.

275. Caviness JN, Hentz JG, Evidente VG, et al. Both early and late cognitive dysfunction affects the electroencephalogram in Parkinson's disease. Parkinsonism Relat Disord 2007;13(6):348-354.

276. Bousleiman H, Zimmermann R, Ahmed S, et al. Power spectra for screening parkinsonian patients for mild cognitive impairment. Ann Clin Transl Neurol 2014;1(11):884-890.

277. Klassen BT, Hentz JG, Shill HA, et al. Quantitative EEG as a predictive biomarker for Parkinson disease dementia. Neurology 2011;77(2):118-124.

278. Caviness JN, Hentz JG, Belden CM, et al. Longitudinal EEG changes correlate with cognitive measure deterioration in Parkinson's disease. J Parkinsons Dis 2015;5(1):117-124.

279. Schlede N, Zimmermann R, Ehrensperger MM, et al. Clinical EEG in cognitively impaired patients with Parkinson's Disease. J Neurol Sci 2011;310(1-2):75-78.

280. Morita A, Kamei S, Mizutani T. Relationship between slowing of the EEG and cognitive impairment in Parkinson disease. J Clin Neurophysiol 2011;28(4):384-387.

281. Zimmermann R, Gschwandtner U, Hatz F, et al. Correlation of EEG slowing with cognitive domains in nondemented patients with Parkinson's disease. Dement Geriatr Cogn Disord 2015;39(3-4):207-214.

282. Kamei S, Morita A, Serizawa K, Mizutani T, Hirayanagi K. Quantitative EEG analysis of executive dysfunction in Parkinson disease. J Clin Neurophysiol 2010;27(3):193-197.

283. Bosboom JL, Stoffers D, Stam CJ, et al. Resting state oscillatory brain dynamics in Parkinson's disease: an MEG study. Clin Neurophysiol 2006;117(11):2521-2531.

284. Bosboom JL, Stoffers D, Wolters E, Stam CJ, Berendse HW. MEG resting state functional connectivity in Parkinson's disease related dementia. J Neural Transm 2009;116(2):193-202.

285. Picton TW, Bentin S, Berg P, et al. Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. Psychophysiology 2000;37(2):127-152.

286. Hanafusa H, Motomura N, Fukai M. Event-related potentials in senile dementia of Alzheimer's type, multiinfarct dementia and Parkinson's disease. Jpn J Psychiatry Neurol 1991;45(3):667-670.

287. Toda K, Tachibana H, Sugita M, Konishi K. P300 and reaction time in Parkinson's disease. J Geriatr Psychiatry Neurol 1993;6(3):131-136.

288. Ito J. Somatosensory event-related potentials (ERPs) in patients with different types of dementia. J Neurol Sci 1994;121(2):139-146.

289. O'Mahony D, Rowan M, Feely J, O'Neill D, Walsh JB, Coakley D. Parkinson's dementia and Alzheimer's dementia: an evoked potential comparison. Gerontology 1993;39(4):228-240.

290. Matsui H, Nishinaka K, Oda M, Kubori T, Udaka F. Auditory event-related potentials in Parkinson's disease: prominent correlation with attention. Parkinsonism Relat Disord 2007;13(7):394-398.

291. Tanaka H, Koenig T, Pascual-Marqui RD, Hirata K, Kochi K, Lehmann D. Event-related potential and EEG measures in Parkinson's disease without and with dementia. Dement Geriatr Cogn Disord 2000;11(1):39-45.

292. Pang S, Borod JC, Hernandez A, et al. The auditory P 300 correlates with specific cognitive deficits in Parkinson's disease. J Neural Transm Park Dis Dement Sect 1990;2(4):249-264.

293. Bodis-Wollner I, Borod JC, Cicero B, et al. Modality dependent changes in event-related potentials correlate with specific cognitive functions in nondemented patients with Parkinson's disease. J Neural Transm Park Dis Dement Sect 1995;9(2-3):197-209.

294. Aotsuka A, Weate SJ, Drake ME, Jr., Paulson GW. Event-related potentials in Parkinson's disease. Electromyogr Clin Neurophysiol 1996;36(4):215-220.

295. Chen KJ, Lin RT, Liu CK, Tai CT, Lai CL. Relationship between event-related potentials and frontal-subcortical dysfunction in Parkinson's disease. Parkinsonism Relat Disord 2006;12(7):453-458.

296. Bokura H, Yamaguchi S, Kobayashi S. Event-related potentials for response inhibition in Parkinson's disease. Neuropsychologia 2005;43(6):967-975.

297. Celebi O, Temucin CM, Elibol B, Saka E. Short latency afferent inhibition in Parkinson's disease patients with dementia. Mov Disord 2012;27(8):1052-1055.

298. Yarnall AJ, Rochester L, Baker MR, et al. Short latency afferent inhibition: a biomarker for mild cognitive impairment in Parkinson's disease? Mov Disord 2013;28(9):1285-1288.

LEYEND FOR TABLES AND FIGURES

Table 1. Summary of the studies that evaluated CSF amyloid ß1-42 (Aß1-42), total tau (t-tau), phosphorylated tau (p-tau), total α-synuclein (t-α-syn), and oligomeric α-synuclein (o-α-syn) as potential biomarkers for PDD or PD-MCI

Table 2. Summary of genetic studies assessing APOE, MAPT and GBA as potential biomarkers of PD-MCI and PDD.

Table 3. Summary of the potential biomarkers of PDD and PD-MCI in function of the pathological processes implicated.

Figure 1. Summary of the potential biomarkers of PDD and PD-MCI found in studies of MRI, PET (cerebral metabolism) and SPECT (regional cerebral blood flow), body fluids, genetic background, and neurophysiology.

Figure 2. Summary of PET and SPECT studies that have assessed cerebral metabolism or regional cerebral blood flow respectively as potential biomarkers of PD-MCI and PDD.

Supplementary table 1. Summary of studies assessing CSF potential biomarkers for PDD and PD-MCI other than neuropathologic proteins and studies assessing potential biomarkers in plasma/serum and urine.

Supplementary table 2. Summary of PiB PET and acetylcholine-related PET and SPECT studies assessing PD-MCI or PDD and those reporting correlations with any cognitive measure in PD, PDND or PDCN.