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Idiopathic Parkinson's Disease, Vascular Risk Factors and Cognition: A Critical Review

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1. Introduction

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system that affects 1.5 million of individuals in the United States (American Parkinson Disease Association, 2011). Although its etiology is still unclear, the degeneration of the dopaminergic neurons in the substantia nigra stands out as the prominent pathological feature (Hauser, 2010). It seems that the balance between the dopamine, acetylcholine and glutamate neurotransmitters is compromised in PD, which may play a role in the subcortical-frontal behaviour impairment (Dubois et al., 1990). Other classical features of PD include the presence of Lewy bodies in the brainstem pigmented neurons, typical characteristics of the α -synucleinopathy in PD (Jellinger, 2003, 2011), and neuronal losses in the *locus coeruleus* (Aarsland et al., 2009).

In addition, the incidence and prevalence of cognitive impairment and dementia, as well as the relative risk for dementia, are higher in PD than in healthy elderly (Aarsland et al., 2001; Aarsland et al., 2005; de Lau et al., 2005); this is thus an important problem. Some clinical and demographical risk factors for cognitive impairment and dementia in PD (PDD) have consistently been reported. More severe motor features such as gait disturbance, rigidity and postural instability tend to predict a faster cognitive decline and thus, an earlier dementia diagnosis (Aarsland et al., 2005; Aarsland & Kurz, 2010). The association of extrapyramidal signs with cognitive impairment supports the hypothesis of a role for PD subcortical pathology in the development of dementia (Levy et al., 2002; Baner et al., 1993). Older age, disease duration and older age at onset were also identified as prominent risk factors for cognitive impairment in PD (Aarsland et al., 2001; Aarsland & Kurz, 2010; Hughes et al., 2000). Other potential features likely to predict cognitive impairment and PDD include visual hallucinations and genetic factors (Aarsland et al., 2010). However, these risk factors and their impact on cognition will not be directly reviewed in the present chapter, as they are considered to be respectively neuropsychiatric and genetic risk factors.

As in Alzheimer's disease (AD) (Petersen, 2004), Mild Cognitive Impairment (MCI) is another potential predictive factor for PDD (Aarsland et al., 2010). In this context, a significant number of non-demented PD patients present with MCI (Aarsland et al., 2010;

Ebmeier et al., 1991; Muslimovic et al., 2005). Some cognitive deficits, notably on tests of memory and executive functions predicted a shorter evolution toward PDD in some studies (Levy et al., 2002; Janvin et al., 2005). Poor performances on tests involving posterior cortical areas such as the semantic fluency test and the copy of a figure test would be the most important predictors of cognitive decline according to some authors (William-Grays et al., 2007). However, the profile of cognitive impairment is heterogeneous, some patients presenting with memory impairment while others show more language, executive and visuospatial impairments (Elgh et al., 2009; Janvin et al., 2005; Uc et al., 2009). Identifying factors contributing to cognitive deterioration is a noteworthy goal because a diminution in quality of life and an augmentation of mortality are associated with cognitive impairment and dementia in PD. Vascular risk factors (VRF) are among those factors. Several studies support the contribution of VRF in elderly adults in the development of vascular dementia and of Alzheimer's disease (Gorelick et al., 2011, for a review; Wiederkehr et al., 2009). Indeed, in the statement for healthcare professionals from the American Heart Association/American Stroke Association, blood pressure, hyperglycemia/diabetes, hypercholesterolemia, stroke, heart disease, alcohol intake and smoking were some of the VRF pointed out as being involved in vascular cognitive impairment, a possible prodromal phase of dementia (Gorelick et al., 2011).

However, there is a controversy regarding the occurrence and impact of the VRF on cognition and on the clinical evolution in PD and there is a lack of systematic review on the topic (Aarsland & Kurz, 2010; Korczyn, 2010). Only one review was found but it was strictly investigating the possible link between elevated (\uparrow) homocysteinemia (Hcy), L-dopa treatment and cognitive dysfunction and dementia in PD but it did not question the possible involvement of other VRF in cognitive impairment in PD (Zoccolella et al., 2010). This article reviewed 16 studies on \uparrow Hcy and cognitive impairment, dementia and neurodegenerative markers in PD (Zoccolella et al., 2010). However, 5 of the studies were only available as abstracts of conference presentations. The current review will thus use more stringent inclusion criteria for articles and will update as well as build upon the data of Zoccolella et al. (2010) regarding hyperhomocysteinemia as a possible VRF for cognitive impairment and dementia in PD. The present work will also review the possible involvement of other VRF such as hypertension (HT), type 2 diabetes mellitus (DM), heart disease (HD), hypercholesterolemia (HCL), stroke history (SH) /transient ischemic attacks (TIA), alcohol intake (ALC) and smoking (SMO) in the development of cognitive impairment and dementia in PD.

In summary, there is currently no consensus regarding the presence of VRF and their impact on cognition in PD. Therefore, the first objective of the current chapter is to perform a critical literature review on the cognitive profile of patients with PD and VRF in order to clarify this issue. The second objective is to investigate the possible biological mechanisms underlying the presence of VRF and cognitive dysfunctions in PD. Finally, some recommendations will be made to improve future research in this area.

2. Method

A search in MEDLINE/PubMed, PsycINFO and AgeLine (EBSCO) databases was conducted using the following keywords: (1) "Parkinson" AND "cognition/cognitive" AND

“vascular risk factors”, (2) “Parkinson” AND “cognition” AND “smoking/tobacco smoking/cigarette” OR “hypertension” OR “hypercholesterolemia” OR “diabetes/diabetes mellitus” OR “homocysteine/hyperhomocysteinemia” OR “alcohol” OR “heart disease. The search included articles published from 1990 to May 31st, 2011. A manual search in the references of the selected articles was also performed as a second step to identify other pertinent publications. The selected articles had to meet the following inclusion criteria: 1) articles had to be published in English or French in order to be reviewed. 2) While longitudinal controlled studies were prioritized, cross-sectional studies with controls and/or using between-patient or within-patient comparisons were also considered. 3) Studies had to not only report VRF in PD, but also had to assess cognition using at least one standardized cognitive measure; and the authors had to report the results of the cognitive assessment. The studies were excluded if they were only case reports. The articles were independently reviewed by the two co-authors and final data were registered following a consensus meeting.

3. Results

3.1 Search results

Eighteen articles published from 1990 to 2010 met the inclusion criteria of the review (Alves et al., 2004; Barone et al., 2008; Camicioli et al., 2009; Hassin-Baer et al., 2006; Haugarvoll et al., 2005; Kandiah et al., 2009; Levy et al., 2002; Marder et al., 1990; Matteau et al., 2010; O’Suilleabhain et al., 2006; Ozer et al., 2006; Rektor et al., 2009; Religa et al., 2006; Rodriguez-Oroz et al., 2009; Slawek et al., 2008; Weisskopf et al., 2007; Zoccolella et al., 2009; Zoccolella et al., 2005). Sixteen articles were rejected because: 5 were only abstracts (Antonini et al., 2006; Litvinenko et al., 2005; Menendez et al., 2007; Shin & Sohn, 2006; Stathis et al., 2006), 6 didn’t report the results of the cognitive assessment or didn’t assess cognition using at least one standardized cognitive measure (Blandini et al., 2001; Ebmeier et al., 1990; Kuhn et al., 1998; Muller et al., 1999; Nakaso et al., 2006; Yasui et al., 2000;) and 5 didn’t assess the effects of vascular risk factors (Aarsland et al., 2004; de Lau et al., 2005; Hughes et al., 1992; Locascio et al., 2003; Papapetropoulos et al., 2006).

3.2 Design and sample size of the studies

Table 1 summarizes the study design and participant’s characteristics in the 18 selected studies. Only 1 study had a randomized double-blind placebo-controlled design (R-DB-PC) since it was a clinical trial on rivastigmine, 1 study had a longitudinal (LON) case-control (CC) design (follow-up of 8 years), 4 studies were longitudinal with between-patient comparisons (BPC) with mean follow-ups ranging from 2.0 to 4.0 years, 6 studies had a case-controlled design, 5 studies were cross-sectional (CS) with between-patient comparisons, and 1 study was cross-sectional using within-patient comparisons (WPC).

The number of PD patients included in the studies ranged from 35 to 342, whereas the number of healthy controls (when applicable, n=7 studies) ranged from 28 to 1144. One study (Alves et al., 2004) had 2 control groups: 100 healthy controls and 100 patients with only diabetes mellitus. The mean (SD) sample size for the 18 selected studies is 124.7 (87.5) PD patients and 229.4 (405.8) healthy controls (HC). However, 9 studies (50%) had <100 PD patients in their samples; and these small sample sizes reduce statistical power.

The PD patient groups were often divided into comparison subgroups with VRF/no-VRF (n=7 studies), dementia/no dementia (n=3 studies), normal cognitive function/mild cognitive impairment/dementia (n=3 studies), cognitive decline/no cognitive decline (n=1 study) and levodopa treated/untreated (n=1 study).

3.3 Participants characteristics

The mean age of PD patients in the 18 studies varied from 59.0 to 75.5 years old. However, PD patients were usually older than 65 years old (11/18 studies). Regarding the gender of patients, only one study didn't report the gender of the subjects (Religa et al., 2006). In most studies (n=15 studies), the male/female ratio was equal. However, one study had a significant greater number of male patients in the VRF compared to the no-VRF group (Haugarvoll et al., 2005) and another study had a significantly greater number of male patients in the two elevated homocysteine groups (Hassin-Baer et al., 2006).

Out of the 18 selected articles, only 7 reported the level of education of the participants in mean years of schooling. Although one study reported education as the percentage of patients having completed primary school (Rodriguez-Oroz et al., 2009) and another study as the percentage of patients having completed an academic degree (Weisskopf et al., 2007), 11 studies didn't report the education level of the participants at all. Among the 7 studies reporting education as the number of years attending school, the mean years of education varied from 5.7 to 15.2 years. Nevertheless, PD patients had at least 10 years of education in 4/7 studies that reported the education level. Therefore, most patients were well-educated. PD patients were recruited in movement disorder centers/clinics (MDC) (9 studies), general hospitals (HOS) (3 studies), community (COM) (2 studies), movement disorder database (MDB) (2 studies) and in multiple centers from different North-American and European countries (MC) (1 study). Only one study didn't report clearly the recruitment location. Healthy controls (HC), when applicable, were recruited in general hospitals in 3 studies and in the community in 3 studies while the recruitment location was not clearly stated in 1 study.

Mean disease duration in PD patients (at baseline when applicable) varied from less than 2 years to 14.7 years. Only one study didn't report the disease duration directly, but specified that it was less than 2 years, because the study focused on newly diagnosed patients (Kandiah et al., 2009).

The Hoehn & Yahr stage (H&Y) is a simple scale to globally assess PD severity (Hoehn & Yahr, 1967): stage 0= no signs of disease; stage 1= very mild symptoms on only one side of the body; stage 1.5= symptoms on only one side of the body with axial involvement; stage 2= symptoms on both sides without balance impairment; stage 2.5= mild symptoms on both sides with recovery on pull test; stage 3= mild to moderate symptoms and potential postural instability with maintenance of independence; stage 4= severe symptoms (patient is severely debilitated and needs assistance but can walk and stand alone); and stage 5=very severe symptoms confining the patients to a wheelchair or a bed unless assisted.

Ten of the 18 selected articles reported the H&Y stage of the PD patients, and it ranged between 2.1 and 3.9. However, one study reported only that patients were equal to or below stage 3.0 (Religa et al., 2006). Another study (Barone et al., 2008) reported H&Y stages with the percentage of patients in each stage, including 54/342 patients in the 4.0-5.0 range,

which was rare in the studies reviewed herein. Nonetheless, the mean H&Y stage was below 3.0 in 7 out of 9 studies; thus most studies included patients in the early stages of PD.

The Unified Parkinson's disease Rating Scale (UPDRS) is a tool designed to assess different clinical aspects of patients in the PD course (Fahn et al., 1987). It allows a comprehensive coverage of motor symptoms and was proved to be valid and reliable (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003). Higher scores are associated with greater disability. Section I (maximum=16 points) assesses mentation, behaviour and mood (4 items). Section II (maximum=52 points) evaluates the activities of daily living (ADL) with 13 items. Section III (maximum=108 points) consists in a motor examination (14 items). Section IV evaluates clinical signs. A total of 13/18 studies reported the UPDRS score of patients. Two studies reported the score for sections I-IV (ranging from 22.9 to 50.9) and only one study reported the total score (I-V). However, most studies (n=10) only reported the motor examination (section III) score. Motor scores ranged from 17.3 to 48.1 in these studies and most of them (n=8 out of 10) had PD patients with a score of 35.0 and lower. In other words, in most studies, patients had mild to moderate motor symptoms. Four studies assessed the UPDRS when patients were "ON", whenever ON-OFF fluctuations were present, while only one study assessed them in the OFF state, and 8 studies didn't specify the procedure.

Table 2 presents the three sets of PD diagnostic criteria that were used in the 18 articles. The United Kingdom Parkinson's Disease Society Brain Research Centre (UKPDSBRC) criteria (Gibb et al., 1988; Hughes et al., 1992) were the most commonly used (n=9 studies), followed by the National Institute of Neurological Disorders and Stroke (NINDS) criteria (Gelb et al., 1999) (n=3 studies) and the Norwegian criteria of Larsen et al. (1994) (n=2 studies). The diagnosis was made only using the clinical impression of neurologists in one study (Weisskopf et al., 2007) and 3 studies didn't specify the diagnostic criteria used.

3.4 Vascular risk factors

Table 3 summarizes the frequency of the different vascular risk factors in the selected studies, their measures and the medication taken by the participants.

3.4.1 Hyperhomocysteinemia (↑Hcy)

Homocysteine (Hcy) is a sulfur-containing amino acid found in blood plasma and naturally biosynthesized as an intermediate product from the demethylation of the amino acid methionine (Reutens & Sachdev, 2002; Stanger et al., 2003). Hcy is metabolized in three distinct pathways (Mattson & Shea, 2003). Two pathways involve remethylation: the first (via the enzyme betaine-homocysteine methyltransferase) occurs in the liver and kidneys while the second (via the enzyme methionine synthase), catalyzed by methylentetrahydrofolate reductase (MTHFR), occurs in all human tissue and requires vitamin B12 and folate as cofactors. A third metabolic pathway involves transsulfuration (via the enzymes cystathionine- β -synthase (C β S) and γ -cystathionase) with vitamin B6 as a cofactor. (Mattson & Shea, 2003; Reutens & Sachdev, 2002).

The American Society of Human Genetics and the American College of Medical Genetics (ASHG/ACMG, 1998) define normal blood plasma level of Hcy as ranging from 5.0 to 15.0

μmol/L and hyperhomocysteinemia as a fasting total plasma Hcy level of >15.0 μmol/L. Plasma Hcy level increases with age and is higher in men than in women. The effect of age is partly explained by the diminution of renal function with increasing age (Stanger et al., 2003).

Hyperhomocysteinemia(↑Hcy) is due to multiple etiologies. Genetic abnormalities in genes encoding for enzymes involved in Hcy metabolism could partially explain an increase in Hcy concentration. Carriers of a thermolabile variant of MTHFR at nucleotide position 667 (MTHFR 677C→T) present a reduced enzymatic activity of MTHFR by approximately 70%, which leads to an increased level of blood plasma Hcy (Stanger et al., 2003). Vitamin deficiencies are probably the main factors of acquired ↑Hcy and can be the consequences of insufficient dietary intake, reduced absorption, increased consumption and drug interactions (Stanger et al., 2003). Some other relevant acquired causes of ↑Hcy include older age, renal failure (impaired remethylation), hypothyroidism (enzyme induction), alcohol intake (interference with B6, B12 and folate + enzyme inhibition) and cigarette smoking (interference with B6, B12 and folate + redox) (Finkelstein, 1998; Reutens & Sachdev, 2002; Stanger et al., 2003).

Levodopa (L-dopa) intake in PD was associated with Hcy blood and plasma levels (Kuhn et al., 1998; Müller et al., 1999; Rogers et al., 2003; Yasui et al., 2000). Levodopa is a substrate for S-adenosyl methionine (SAM)-dependent methylation. In fact, levodopa O-methylation to 3-O-methyldopa by catechol-O-methyltransferase (COMT) constitutes a main metabolic pathway (Müller et al., 2002). COMT converts S-adenosylmethionine to S-adenosylhomocysteine which will eventually become Hcy. Therefore, ↑Hcy in PD is most likely the consequence of S-adenosylhomocysteine formation during levodopa breakdown (Müller et al., 2001, 2002).

Some studies also support a genetic role in ↑Hcy in PD: blood plasma levels are elevated in levodopa-treated patients homozygous for the MTHFR C667T mutation (Kuhn et al., 2001; Todorovic et al., 2006; Yasui et al., 2000). Hcy has also been involved in multiple biological mechanisms and notably as a neurotoxin contributing to neurodegeneration. Hcy is linked to increased oxidative stress, excitotoxicity, promotion of cellular apoptosis and the promotion of the pathophysiological processes of Alzheimer's like disease (Sachdev, 2005).

A total of 9 studies reported total Hcy levels in the PD groups and the number of PD patients with ↑Hcy ranged from 17 to 247. Only two studies didn't report the number of hyperhomocysteinemic patients. Nevertheless, the number of PD patients with ↑Hcy was below 31 in 5/7 studies, which are rather small groups.

3.4.2 Smoking (SMO)

Smoking is associated with cardiovascular disease and is potentially a VRF for cognitive impairment because its pathological mechanisms are known to increase oxidative stress, to increase inflammation and to promote thrombosis and atherosclerotic processes (Ambrose & Barua, 2004; Swan & Lessov-Schlaggar, 2007). Cigarette smoking reduces blood circulation by narrowing the arteries and thus, puts tobacco users at higher risk of developing peripheral vascular disease. Light and heavy smoking also results in a detrimental effect on endothelial vasoregulatory activity, thus leading to increased cardiovascular risk (Barua et al., 2002).

A total of 9 studies reported smoking in the PD patients. The number of PD patients who ever smoked (past + current smokers) varied from 10 to 78. However, the number of smokers is unknown in 2/9 studies. Only one study included smoking HC (n=49) (Alves et al., 2004). The distinction between past smokers and current smokers is clear in only 2 studies.

3.4.3 Diabetes Mellitus – Type 2 Diabetes (DM)

Type 2 diabetes mellitus (DM) is a metabolic disorder characterized by high blood glucose in the context of insulin resistance and insulin deficiency. Hyperglycemia is associated with functional changes in cerebral blood flow (Cosentino et al., 2009). Although the mechanism underlying the link between DM and cognitive impairment and dementia is still not well understood, it likely involves several inter-related processes. DM is thus a risk factor for stroke (Stegmayr & Asplund, 1995) and it is also assumed to be a risk factor for vascular dementia (Skoog, 1994; Tatemichi et al., 1993). Some biological links have also been described between DM and AD, such as indications of advanced glycation end-products (AGE) and increased AGE receptor expression in brains of patients with AD. As AGEs are known to be involved in DM complications, diabetes might thus influence AD brain pathology (Yan et al., 1997), and AD pathogenesis can be present in PD and PDD.

A total of 8 studies reported DM in PD and the number of PD patients with DM varied from 3 to 16. Out of these, the number of PD patients with DM is unknown in 3/8 studies. Another study (Alves et al., 2004) had 100 control participants with DM but not with PD.

3.4.4 Arterial Hypertension (HT)

A normal blood pressure (nBP) is required to maintain cognitive functioning, because it contributes to adequate cerebral perfusion. Hypertension (HT) is not only an important risk factor for strokes and heart disease; it is also an immediate risk factor for cognitive impairment and vascular dementia (Breteler, 2000). Individuals suffering from HT have stiffer artery walls and increased blood vessel resistance. This requires the heart to work harder in order to pump the blood, thus increasing the pressure of the blood leaving the heart and consequently increasing the risk of cerebrovascular ischemic damage (Chobanian et al., 2003). Blood pressure is often classified in different stages. According to the American Heart Association (Chobanian et al., 2003), nBP is defined as systolic pressure (SP) of 90-119 mmHg and diastolic pressure (DP) of 60-79 mmHg. Prehypertension is characterized by SP=120-139 mmHg and DP=80-89 mmHg, stage 1 hypertension by SP=140-159 mmHg and DP=90-99 mmHg, and stage 2 hypertension as SP \geq 160 mmHg and DP \geq 100 mmHg (Chobanian et al., 2003).

A total of 10 studies reported arterial HT in PD. The number of PD patients with HT varied from 14 to 68, and was generally below or equal to 40 patients (n=6 studies). However, 3/10 studies didn't report the exact number of PD patients with HT.

3.4.5 Heart Diseases (HD)

Commonly included in the heart disease (HD) category are coronary heart disease, heart failure and atrial fibrillation (AF). Coronary heart disease consists in the narrowing by

atherosclerosis of the blood vessels that supply blood, nutrients and oxygen to the heart. Therefore, the consequent limitation of the blood flow to the heart muscle is responsible for ischemia. Coronary heart disease is one of the most common causes of heart failure (American Accreditation Health Care Commission (A.D.A.M.) Medical Encyclopedia, 2011). Heart failure is a condition in which the heart can no longer pump enough blood to every body part (Jessup et al., 2009). Systolic heart failure is characterized by insufficient blood ejection out of the heart while diastolic heart failure consists in heart muscles harder to fill up with blood. AF consists in a problem with the contraction rhythm of the atria that causes the blood to be ineffectively pumped to the ventricles. Hence, the arrhythmia is responsible for irregular blood flow throughout the whole body. AF is also a risk factor for heart failure (National Collaborating Centre for Chronic Conditions, 2006). Moreover, some studies reported that atrial fibrillation is associated with a higher risk for conversion to dementia in MCI non-PD patients (Ravaglia et al., 2006).

A total of 6 studies reported heart diseases in PD. The number of PD patients with HD ranged from 14 to 28, but the number is unknown in 2/6 studies. Four out of 6 studies included coronary heart disease in the HD category with n of PD patients varying from 9 to 17 (unknown in 2 studies). Atrial fibrillation (AF) and heart failure were reported in 2 studies: in one of these studies, only one patient was affected by AF, and 9 patients had heart failure, whereas the numbers for AF and heart failure are unknown in the other study.

3.4.6 Hypercholesterolemia (HCL)

Hypercholesterolemia (HCL) is a form of dyslipidemia defined as an abnormal amount of lipids in the blood, and is an established VRF for dementia (Luschinger et al., 2005). The mechanisms underlying the role of HCL in the development of dementia are not clearly understood. However, there is evidence that cholesterol alters the degradation of amyloid precursor protein and shows an effect on amyloid fibril formation, which may play a role in the pathogenesis of AD (Sponne et al., 2004). Amyloid abnormalities were described in the brains of PD patients with cognitive impairment (Braak & Braak, 1990) as well as of PDD patients (Nobili et al., 2011). Therefore, HCL could be a VRF for cognitive impairment and PDD, via its possible contribution to amyloid aggregation.

Three studies reported HCL in PD patients but only 2 studies mentioned the number of patients presenting with this condition (n=16 and 34).

3.4.7 Stroke History (SH) / Transient Ischemic Attacks (TIA)

The link between stroke and cognitive impairment and dementia is very well known (Chui et al., 1992; Roman et al., 1993). A stroke in any higher processing cerebral area will inevitably cause cognitive dysfunctions. One of the strongest predictors of cognitive decline after an initial stroke is the occurrence of a second stroke (Gorelick et al., 2011).

Only 4 studies reported a stroke history (SH) or transient ischemic attacks (TIA) and the number of patients with this VRF varied from 2 to 5 in 3 studies; one study didn't indicate the number of patients with this VRF.

3.4.8 Alcohol (ALC)

Observational studies have shown that alcohol consumption might be related to Hcy in a J-shaped fashion: chronic consumers (alcoholics) have very high levels of Hcy and moderate alcohol consumers (≤ 4 glasses/day) have lower Hcy levels as compared to non-drinkers (De Bree et al., 2001). Therefore the rationale for considering alcohol as VRF for cognitive impairment in PD might be partly explained by its deleterious effect on Hcy levels. It also lowers vitamin B12 and folate levels (Gibson et al., 2008).

Only 3 studies reported alcohol intake and the number of PD patients consuming alcohol was unknown in one study, $n=7$ in another, and another study distinguished 44 former and 29 current consumers.

3.5 Medication

L-Dopa was the most common medication taken by PD patients ($n=14$ studies) and doses varied from 326.7 to 1028.0 mg/day with a mean of 589 mg/day. Other medications included dopamine agonists ($n=5$ studies) and anticholinergics ($n=3$ studies). Only one study reported the use of antipsychotic and antidepressant drugs. Thus the groups included in this review were generally neither depressed nor psychotic. Only 3/18 studies didn't report the medication taken by the PD patients.

3.6 Cognition and VRF

Results and tests of the neuropsychological assessment in the 18 studies are illustrated in Table 4. Cognitive tests are grouped under specific cognitive domains and are presented below, starting from the most prevalent to the least prevalent in the studies.

Global cognitive function was assessed in 17/18 studies and the most administered tests were the Mini-Mental State Examination (MMSE) ($n=15$ studies) and the Dementia Rating Scale (DRS) ($n=3$ studies). Intelligence (global cognitive function) was also evaluated in one study using the Wechsler-Bellevue Intelligence Scale (WBIS). However, no association with the VRF could be made, since the authors used the WBIS only to assess the premorbid cognitive state of the patients. The other tests assessing global cognitive function were only used once (see Table 4).

3.6.1 Association between VRF and risk for dementia (global measure of dementia)

Six studies investigated the association between VRF and the risk of incident dementia in PD. Dementia was generally assessed using MMSE in 5/6 studies (see Table 4). Zoccollella et al. (2009) found that Hcy levels were significantly higher in the PDD group compared to the PD group without dementia. The risk for dementia in the \uparrow Hcy group was significantly higher than in the <12.4 $\mu\text{mol/L}$ (normal Hcy) group. A multivariate logistic regression showed that \uparrow Hcy was associated with presence of dementia. However, Rodriguez-Oroz et al. (2009) found that Hcy levels didn't predict the cognitive status of PD patients.

Levy et al. (2006) found that current and ever smoking were associated with a higher risk for PDD, but past smoking was not. They also reported that smokers who stopped smoking less

than 8 years before PD onset had a higher risk for PDD. However, pack-years of smoking and smoking duration weren't associated with a higher risk for PDD.

Zoccolella et al. (2009) found that HT was significantly more frequent in the PDD group compared to the PD group without dementia. Haugarvoll et al. (2005) found that PDD had more heart failure than patients without dementia after a 4-year follow-up. Slawek et al. (2008) demonstrated that HD was significantly more prevalent in the PDD group compared to the cognitively normal PD patients, though it was only a weak predictive factor for dementia.

However, results of various regression analyses did not find heart failure, coronary HD, AF, stroke, TIA, HT, DM, HCL, ALC and SMO to be predictive of dementia (Haugervoll et al., 2005; Levy et al., 2006; Marder et al., 1990; Slawek et al., 2008; Zoccolella et al., 2009).

3.6.2 Association between VRF and a score of global cognition

↑Hcy in PD patients was associated with worse global cognition per the MMSE compared to patients with normal Hcy in only 2 studies (Religa et al., 2006; Zoccolella et al., 2005), but there was no difference between L-dopa-treated and non-L-dopa treated patients (Religa et al., 2006).

Six studies (Barone et al., 2008-at baseline only); Camicioli et al., 2009; Hassin-Baer et al., 2006; O'Suilleabhain et al., 2004, 2006; Ozer et al., 2006; Rodriguez-Oroz et al., 2009) found no association between ↑Hcy and worse global cognition as measured by the MMSE (n=5 studies), the ADAS-Cog (n=1), the BDS (n=1), the DRS (n=1) and the STMS (n=1 study). However, the R-DB-PC study of Barone et al. (2008) found that ↑Hcy-rivastigmine-treated patients significantly improved their performance after 24 weeks on the ADAS-Cog and the MMSE compared to ↑Hcy-placebo-treated-patients. This improvement wasn't present in the normal/low Hcy groups, suggesting a relationship between cognition, ↑Hcy and successful treatment with a cholinesterase inhibitor (rivastigmine). Interestingly, O'Suilleabhain et al. (2004, 2006) only found a significant difference between the PD group with Hcy ≥14 μmol/L compared to the PD with Hcy <14 μmol/L when they pooled together the results of all neuropsychological tests (14). However, ↑Hcy at baseline was not associated with a greater decline on the pooled scores 2 years later.

Two studies reported some kind of relationship between smoking in PD patients and poor cognition. Weisskopf et al. (2007) found that smoking was associated with worst global cognition (per the TICS), and the risk for cognitive impairment was significantly higher for current smokers compared to never smokers. In the study of Matteau et al. (2010), patients with VRF (smoking in the past 10 years, myocardial infarct, stroke, DM and HT) performed significantly more poorly on the MMSE compared with no-VRF patients, independently of disease duration. In this particular study, the most prevalent VRF (in 66% of PD patients) was a history of smoking in the past 10 years, suggesting a possible relationship between smoking and global cognition in PD.

However, smoking and global cognitive function were not associated together in 4 studies with cross-sectional analyses and at 4 and 8-year follow-ups in one study. In addition, there was no difference between PD non-smokers, all smokers and heavy smokers (20 pack-years and more) on cognition (Alves et al., 2004; Marder et al., 1990). In another study, the MMSE

score of PD patients was associated with an increase of intimomedial thickness (an indicator of large vessel impairment) but not with smoking, HT, DM, ischemic HD and stroke (Rektor et al., 2009).

Finally, Slawek et al. (2008) found that coronary HD was associated with a lower score on the MMSE, whereas Kandiah et al. (2009) found that diabetes mellitus didn't predict cognitive decline as measured by the MMSE.

3.6.3 Episodic memory

Episodic memory was assessed in 10 studies and the most administered tests were the Benton Visual Retention Test (BVRT) (n=2 studies), the Rey Auditory Verbal Learning Test (RAVLT) (n=2 studies) and memory subtests of the Wechsler Memory Scale (WMS) (n=2 studies). All other tests assessing episodic memory were only used once (see Table 4).

Ozer et al. (2006) found significant lower scores on the Sozel Bellek Surecleri Test (SBST) - delayed recall (verbal memory) in the PD group with Hcy ≥ 14 $\mu\text{mol/L}$ compared to PD with Hcy < 14 $\mu\text{mol/L}$, but not on the visual memory subtest of the WMS. In the study of O'Suilleabhain et al. (2004, 2006), PD with Hcy ≥ 14 $\mu\text{mol/L}$ significantly declined on the Rey-Osterrieth-Complex-Figure (ROCF)-immediate recall at 2-year follow-up, whereas PD with Hcy < 14 $\mu\text{mol/L}$ did not. However, the baseline performances of these patients were comparable on episodic memory measures.

Two studies assessing episodic memory did not find significant differences or correlations between patients Hcy levels and measures of episodic memory (Hassin-Baer et al., 2006; Rodriguez-Oroz et al., 2009).

Coronary heart disease was associated with a lower score on the RAVLT, a measure of verbal episodic memory (Slawek et al. 2008) whereas an increased intimomedial thickness and pulsatility index (an indicator of small vessel impairment) were correlated with the WMS-III- Recognition-word list II (Rektor et al., 2009).

There was no association between the presence of SMO (Rektor et al., 2009; Slawek et al., 2008; Weisskopf et al., 2007), HT, DM, ischemic heart disease, HCL, stroke, and alcohol intake and measures of episodic memory (Rektor et al., 2009; Slawek et al., 2008).

3.6.4 Executive functions

Executive functions were assessed in 10 studies and the most administered tests were the Stroop (n= 4 studies), the Frontal Assessment Battery (FAB) (n=4 studies) and the Trail Making Test (TMT) (n=2 studies). All other tests assessing executive functions were used only once (see Table 4).

Ozer et al. (2006) found significant lower scores on the Stroop and Wisconsin Card Sorting Test (WCST) in PD with Hcy ≥ 14 $\mu\text{mol/L}$ compared to PD with Hcy < 14 $\mu\text{mol/L}$. However, 4 studies registered no association between Hcy levels and executive functions: on the Stroop test (O'Suilleabhain et al. 2004; Rodriguez-Oroz et al., 2009), even after 2 years of follow-up (O'Suilleabhain et al., 2006); and on the TMT and the Raven Progressive Matrices (Hassin-Baer et al., 2006; Rodriguez-Oroz et al., 2009).

Slawek et al. (2008) found no association between the Tower of Toronto score and the presence of HT, DM, HCL, HD, smoking and alcohol intake. Haugarvoll et al. (2005), Levy et al. (2002) and Camicioli et al. (2009) didn't report results on tests of executive functions in relation with VRF.

3.6.5 Language

Language was assessed in 10 studies and the most administered tests were verbal fluency tests (VFT; category and letter; n=7 studies) and the Boston Naming Test (BNT) (n=2 studies). All other tests assessing language were used only once (see Table 4).

In the R-DB-PC study of Barone et al. (2008), ↑Hcy-rivastigmine-treated patients improved significantly on letter fluency after 24 weeks compared with ↑Hcy-placebo-treated patients, and this improvement wasn't present in the normal/low homocysteine groups. Moreover, O'Suilleabhain et al. (2004, 2006) found that PD patients with Hcy ≥ 14 $\mu\text{mol/L}$ compared to those with Hcy < 14 $\mu\text{mol/L}$ had significantly lower score on verbal fluency at baseline, but the scores of the 2 groups were comparable at follow-up. However, other studies found no association between Hcy levels and scores of verbal fluency (Hassin-Baer et al., 2006; Ozer et al., 2006; Rodriguez-Oroz et al., 2009) and of the BNT (Rodriguez-Oroz et al., 2009).

Verbal fluency scores were significantly associated with an increase of intimomedial thickness and of the pulsatility index (Rektor et al., 2009), as well as with coronary HD (Slawek et al., 2008).

However, verbal fluency scores were not associated with presence of smoking, HT, DM, ischemic heart disease and stroke (Rektor et al., 2009). Levy et al. (2002) and Camicioli et al. (2009) didn't report results on language tests.

3.6.6 Attention and vigilance

Attention and vigilance were assessed in 5 studies and the most administered test was Digit Span (n= 4) while the CDR Computerized Assessment System Power of Attention test (CDR-PoA) was only administered once. The R-DB-PC study of Barone et al. (2008) found that ↑Hcy-rivastigmine-treated patients had a significant improvement on the CDR-PoA after 24 weeks compared to ↑Hcy-placebo-treated patients, and this improvement wasn't present in the rivastigmine and placebo-treated Hcy-normal groups.

However, in other studies, PD with Hcy ≥ 14 $\mu\text{mol/L}$ and PD with Hcy < 14 $\mu\text{mol/L}$ had comparable performances on Digit Span at baseline (Hassin-Baer et al., 2006; O'Suilleabhain et al., 2004; Rodriguez-Oroz et al., 2009;) and 2 years later (O'Suilleabhain et al., 2006).

3.6.7 Visual perception

Visual perception was assessed in 3 studies using the Benton Judgment of Line Orientation (BJLO) test (n=2 studies), the Benton Face Recognition (BFR) test (n=1 study) and the matching part of the Benton Visual Retention Test (BVRT) (n=1 study).

Ozer et al., 2006 reported a significant negative correlation between the concentration of Hcy and the BFR. Results on the BVRT (Levy et al., 2002) and on the BJLO (Haugervoll et al., 2005) were not reported.

Authors	Design	FU (yrs)	n of participants		Participants' characteristics									
			Total	HC	PD (main group and subgroups)	Age (mean in yrs)	M/F	Education (mean in yrs)	Recruited in	PD duration (mean in yrs)	H&Y stage	UPDRS score	PD diagnostic criteria	
Barone et al. (2008) & Emre et al. (2004) (same trial)	R-DB-PC	0.46 (24 weeks)	342	-	Total PD=342 <i>Hcy levels (subgroups)</i> ≥14 μmol/L (n= 247) <14 μmol/L (n=95)	→ → →	- 73.3 71.3	- 167/80 56/39	? ? ?	MC MC MC	? 10.2 8.9	? 1-3=83% 4-5=17% 1-3=87% 4-5=13%	? 34.0 III 31.0 III	UKPDSBRC criteria & DSM-IV criteria (for dementia)
Alves et al. (2004)	LON CC	8.0	439	100 HC + 100 DM	(HC) Total PD=239 <i>SMO=78</i> <i>no-SMO=161</i>	→ → →	72.8 73.4 71.9 74.1	51/49 117/122 60/18 57/104	? ? ? ?	HOS HOS HOS HOS	- ? 9.5 9.0	- ? 2.7 2.9	- ? 46.0 I-IV 50.9 I-IV (both on)	Larsen et al. (1994)
Haugarvoll et al. (2005)	LON BPC	4.0	BL= 171 FU=130	-	Total PD=171 <i>VRF=100</i> <i>no-VRF=71</i>	→ → →	? 72.0 70.0	84/87 56/44 28/43	? 9.5 9.5	COM COM COM	? 9.0 9.0	? 2.4 2.4	? 24.0 I-IV 22.9 I-IV	Larsen et al. (1994)
Kandiah et al. (2009)	LON BPC	2.8 (mean)	106	-	Total PD=106 <i>CD=33</i> <i>no-CD=73</i>	→ → →	61.2 65.0 59.0	62/44 15/18 47/26	7.1 5.0 8.0	MDD MDD MDD	? ? ?	2.1 2.2 2.1	19.8 III 20.0 III 19.0 III	NINDS criteria
Levy et al. (2002)	LON BPC	3.6 (mean)	180	-	Total PD=180 <i>DEM=52</i> <i>no-DEM=128</i>	→ → →	71.0 74.6 69.5	83/97 29/23 54/74	11.1 9.4 11.8	COM COM COM	6.3 7.3 5.9	? ? ?	25.0 III 32.0 III 22.2 III	UKPDSBRC criteria
O'Suilleabhain et al. (2004) [BL]	LON BPC	2.0	BL=97	-	Baseline Total PD= 97 <i>Hcy<14 μmol/L; n=66</i> <i>Hcy≥14 μmol/L; n= 31</i>	→ → →	65.0 64.0 68.0	68/29 43/23 25/6	? ? ?	MDC MDC MDC	3.6 3.6 3.8	? ? ?	? 23.0 III 28.9 III	NINDS criteria
&					Follow-up Total PD=79 <i>Hcy<14 μmol/L; n=54</i> <i>Hcy≥14 μmol/L; n=25</i>	→ → →	67.0 ? ?	55/24 ? ?	? ? ?	MDC MDC MDC	5.5 ? ?	? ? ?	? 22.9 III 31.0 III	

Table 1. Study Design and Participant’s Characteristics

Authors	Design	FU (yrs)	n of participants			Participants' characteristics					
			Total	HC	PD (main group and subgroups)	Age (mean in yrs)	M/F	Education (mean in yrs)	Recruited in	PD duration (mean in yrs)	
Rodriguez- Oroz et al. (2009)	CC	-	119	30	(HC)	→	68.5	16/14	?	COM	?
					Total PD=89	→	?	?	?	MDC	?
					CN=37	→	69.9	20/17	?	MDC	14
					MCI=22	→	70.2	14/8	?	MDC	13
					PDD=30	→	74.9	18/12	?	MDC	14
Weisskopf et al. (2007)	CC	-	1430	1144	(HC)	→	72.2	466/678	?	COM	?
					Total PD=286	→	71.9	137/149	?	COM	6
Zoccolella et al. (2009)	CC	-	275	154	(HC)	→	68.7	97/57	?	HOS	?
					Total PD=121	→	67.4	72/49	?	MDC	?
					PDD=42	→	71.2	27/15	5.7	MDC	10
					no-PDD=79	→	65.4	45/34	7.9	MDC	10
Religa et al. (2006)	CC	-	214	100	(HC)	→	71.2	?	?	HOS	?
					Total PD=114	→	?	?	?	COM	?
					L-dopa= 99	→	70.5	?	?	MDC	6
					Untreated= 15	→	66.0	?	?	MDC	1
Ozer et al. (2006)	CC	-	67	28	(HC)	→	61.9	15/13	?	?	?
					Total PD= 39	→	67.0	25/14	?	MDC	6
					Hcy>14 μmol/L; n=17	→	68.5	?	?	MDC	?
					Hcy<14 μmol/L; n=22	→	64.4	?	?	MDC	?
Camicioli et al. (2009)	CC	-	101	50	(HC)	→	71.6	29/21	15.0	COM	?
					Total PD=51	→	71.5	30/21	13.9	MDC	8
Hassin-Baer et al. (2006)	CS BPC	-	72	-	Total PD=72	→	68.7	46/26	12.0	MDC & Neurology Service	6
					Hcy <12.5 mol/L; n=23	→	69.9	10/12	10.9		5
					12.5-16.7 μmol/L; n=24	→	67.0	18/6	13.2		6
					Hcy >16.7 μmol/L; n=25	→	69.3	18/7	11.8		8

Table 1. Study Design and Participant’s Characteristics (continued)

Authors	Design	FU (yrs)	n of participants			Participants' characteristics					
			Total	HC	PD (main group and subgroups)	Age (mean in yrs)	M/F	Education (mean in yrs)	Recruited in	P duration (mean in yrs)	
Matteau et al. (2010)	CS BPC	-	124	-	Total PD=124	→	?	?	?	MDD	7
					<i>VRF: 67</i>	→	63.9	49/18	12.8	MDD	5
					<i>no-VRF: 57</i>	→	61.3	39/18	15.2	MDD	8
Ślawek et al. (2008)	CS BPC	-	60	-	Total PD=60	→	68.4	35/25	?	MDC	8
					<i>CN: 17</i>	→	64.5	?	?	MDC	6
					<i>MCI: 25</i>	→	68.6	?	?	MDC	9
					<i>PDD: 18</i>	→	71.7	?	?	MDC	9
Zoccolella et al. (2005)	CS BPC	-	35	-	Total PD=35	→	?	25/10	?	?	?
					<i>CogI: 14</i>	→	67.8	10/4	?	?	10
					<i>CN: 21</i>	→	63.7	15/6	?	?	9
Marder et al. (1990)	CS BPC	-	71	-	Total PD=71	→	?	53/18	?	HOS	?
					<i>PDD: 17</i>	→	75.5	17/0	?	HOS	11
					<i>no-PDD: 54</i>	→	64.0	36/18	?	HOS	8
Rektor et al. (2009)	CS WPC	-	57	-	Total PD=57	→	68.2	39/18	?	MDC	9

UKPDSBRC criteria (Gibb et al., 1988)	NINDS criteria (Gelb et al., 1999)	“Norwegian” criteria (Larsen et al., 1992)
<p>Step 1 - Diagnosis of Parkinsonism Bradykinesia At least one: muscular rigidity, 4-6 Hz rest tremor, postural instability not caused by primary visual, vestibular or proprioceptive dysfunction.</p> <p>Step 2 - Exclusion criteria for PD History of repeated strokes with stepwise progression of parkinsonian features History of repeated head injury History of definite encephalitis Oculogyric crises Neuroleptic treatment at onset of symptoms More than one affected relative Sustained remission Strictly unilateral features after 3 years Supranuclear gaze palsy Cerebellar signs Early severe autonomic involvement Early severe dementia with disturbance of memory, language and praxis Babinski sign Presence of cerebral tumor or communicating hydrocephalus on CT scan Negative response to large doses of levodopa (if malabsorption excluded) MPTP exposure</p> <p>Step 3 - Supportive prospective positive criteria for PD (3 or more required for diagnosis of definite IPD)</p> <p>Unilateral onset Rest tremor present Progressive disorder Persistent asymmetry affecting side of onset most</p>	<p>Grouping of clinical features of Parkinson’s disease according to diagnostic utility</p> <p>Group A: characteristic of PD</p> <ul style="list-style-type: none">- Resting tremor, Bradykinesia, Rigidity, Asymmetric onset <p>Group B: suggestive of alternative diagnoses</p> <ul style="list-style-type: none">- Features unusual early in the clinical course: prominent postural instability in the first 3 years after symptoms onset, freezing phenomena in the first 3 years, hallucinations unrelated to medications in the first 3 years, dementia preceding motor symptoms or occurring in the first year- Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades- Severe, symptomatic dysautonomia unrelated to medications- Documentation of a condition known to produce parkinsonism and plausibly connected to the patient’s symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months) <p>1) Criteria for POSSIBLE diagnosis of PD At least 2 of the 3 features in Group A are present and at least 1 of these is tremor or bradykinesia. and Either none of the feature in Group B is present Or symptoms have been present for less than 3 years, and none of the features in Group B is present to date and Either substantial and sustained response to levodopa or a dopamine agonist has been documented Or patients has not had an adequate trial of levodopa or dopamine agonist</p>	<p>1) Criteria for POSSIBLE diagnosis of PD</p> <ul style="list-style-type: none">- Presence of at least two of the following signs: resting tremor, akinesia/bradykinesia, rigidity, postural abnormality- Moderate response to dopamine agonist- At onset of disease absence of significant changes on CT or MRI other than diffuse cortical atrophy or mild hyperintense periventricular foci on MRI. Mild/moderate dementia and autonomic failure which still may be compatible with Parkinson’s disease. Absence of pyramidal and cerebellar signs, as well as environmental factors like drugs and toxic substances and a history of encephalitis that may cause a symptomatic parkinsonism. <p>2) Criteria for PROBABLE diagnosis of PD Type A: Patients with bilateral onset of signs and who fulfill the following I, II and III criteria. Type B: Patients with unilateral onset and who fulfill criteria I, II and IV. Type C: Patients with unilateral onset and who fulfill criteria I, III and V.</p> <p>I. Presence of at least two of the following signs: resting tremor, akinesia/bradykinesia, rigidity, postural abnormality</p> <p>II. Good/excellent response to dopamine agonist.</p> <p>III. At onset of disease absence of significant changes on CT or MRI other than diffuse cortical atrophy or mild hyperintense</p>

<p>Excellent (70-100%) response to levodopa</p> <p>Severe levodopa-induced chorea</p> <p>Levodopa response for 5 years or more</p> <p>Clinical course of 10 years or more</p>	<p>2) Criteria for PROBABLE diagnosis of PD</p> <p>At least 3 of the 4 features in Group A are present</p> <p>and</p> <p>None of the features in Group B is present (symptom duration of at least 3 years is necessary to meet this requirement)</p> <p>and</p> <p>Substantial and sustained response to levodopa or a dopamine agonist has been documented</p> <p>3) Criteria for DEFINITE diagnosis of PD</p> <p>All criteria for POSSIBLE diagnosis of PD are met</p> <p>and</p> <p>Histopathologic confirmation of the diagnosis is obtained at autopsy</p> <p>Proposed criteria for Histopathologic confirmation of Parkinson Disease</p> <ul style="list-style-type: none">- Substantial nerve cell depletion with accompanying gliosis in the substantia nigra- At least 1 Lewy body in the substantia nigra or in the locus coeruleus (note: it may be necessary to examine up to 4 non-overlapping sections in each of these areas before concluding that Lewy bodies are absent)- No pathological evidence for other diseases that produce Parkinsonism (eg progressive supranuclear palsy, multiple system atrophy, cortical-basal ganglionic degeneration) (Note: in excluding other diseases that produce Parkinsonism, published consensus criteria should be used when available)	<p>periventricular foci on MRI. Absence of clinical exclusion criteria like dementia, pyramidal and cerebellar signs and autonomic failure which may indicate another neurodegenerative disorder. Absence of environmental factors like drugs and toxic substances and a history of encephalitis that may cause a symptomatic parkinsonism.</p> <p>IV. Unilateral onset of symptoms and asymmetrical development of disease. Presence of mild dementia or autonomic failure. Otherwise, as in III.</p> <p>V. Unilateral onset of symptoms and asymmetrical development of disease. Moderate response to dopamine agonist.</p> <p>3) Criteria for DEFINITE diagnosis of PD</p> <p>Presence of resting tremor and at least two of the following signs: akinesia/bradykinesia, rigidity, postural abnormality</p> <p>Unilateral onset of signs and asymmetrical development of the disease.</p> <p>Good/excellent response to dopamine agonist.</p> <p>At onset of disease absence of significant changes on CT or MRI other than mild diffuse cortical atrophy or mild hyperintense periventricular foci on MRI. Absence of clinical exclusion criteria like dementia, pyramidal and cerebellar signs and autonomic failure which may indicate another neurodegenerative disorder. Absence of environmental factors like drugs and toxic substances and a history of encephalitis that may cause a symptomatic parkinsonism.</p>
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Table 2. The Diagnostic Criteria for PD

Authors	n of IPD patients presenting with this VRF						VRF Measures		Medication	
	↑Hcy	SMO	DM	HT	HD	HCL	SH/TIA	ALC		
Barone et al. (2008) & Emre et al. (2004)	247	-	-	Yes; n=? + orthostatic hypotension; n=? (192 with vascular disorders)	-	-	-	-	- Blood plasma level: - High: ≥ 14 μmol/L = ↑Hcy - Low or normal: < 14 μmol/L = ↓Hcy	Hcy level (group) ≥14 μmol/L <14 μmol/L 727.3 671.6 4.9 5.3 30.0% 24.2% 29.6% 34.7% 22.3% 26.3% - Mean exposures to rivastigmine and placebo= respectively 20.7 and 22.3 weeks - Rivastigmine: mean dose at week 24 = 7.8 mg/d
Alves et al. (2004)	-	PD: 78 HC: 49	-	-	-	-	-	-	- Pack-years of smoking (average number of cigarette per day divided by 20 and multiplied by years of smoking) - Medical examination & questionnaires	- L-dopa 491.0 mg/d - SMO: 505.0 mg/d - no-SMO:
Haugarvoll et al. (2005)	-	45	3	16	19	-	2	-	- Interviews with patients (cross-checked with medical records)	- L-dopa - VRF : 494.0 mg/d - no-VRF : 532.0 mg/d
Kandiah et al. (2009)	-	-	?	-	-	-	-	-	- Not specified	- L-dopa (n=78) [? mg/d] - DAA (n=49) [? mg/d] - Anti-ACh (n=14) [? mg/d]
Levy et al. (2002)	-	Curr.:10 Past: 69	16	68	-	-	-	Curr.: 29 Past: 44	- Pack-years of smoking - Smoking duration (in years) - Smoking cessation (in years before onset, if applicable) - Questionnaires (BL) & Interviews (FU)	- L-dopa - Total: 354.1 mg/d - PDD: 326.7 mg/d - no-PDD: 364.2 mg/d - Anti-Ach (n=28)
O'Suilleabhain et al. (2004, 2006)	31	BL: - FU: -	-	-	-	-	-	-	- Interviews (for HT, HS, HD, DM) - Blood plasma level: - ↑Hcy= > 1.89 mg/L or >14 μmol/L - B12, folate, creatinine and L-dopa - Polymorphisms in MTHFR CC,CT,TT	- Baseline L-dopa (n=54) - Total: 532.0 mg/d - Follow-up L-dopa (n=57) - nHcy: 377.0 mg/d - ↑Hcy: 754.0 mg/d
Rodriguez-Oroz et al. (2009)	?	-	-	-	-	-	-	-	- Hcy, B12 & B6 and folic acid plasma MRI (n= 101)/CT scan (n= 18) looking for WMH [Wahlund Scale] - Polymorphisms in genes related to HCY metabolism (MTHFR, MTR, MTRR & CBS)	- L-dopa - PD-CN : 786.1 mg/d - PD-MCI : 825.0 mg/d - PDD : 811.3 mg/ - DAA (n=53) [? mg/d] (n) - Pramipexol (25),Ropinirol (14), Cabergoline (10), Pergolide (4)
Weiskopf et al. (2007)	-	Curr.: 16 Past: 112	-	-	-	-	-	-	- Pack-years of smoking - Questionnaires	?

Zoccolella et al. (2009)	?	-	-	40	-	-	-	-	-	-	Blood level of Hcy, B12 and folate
Religa et al. (2006)	214	-	-	-	-	-	-	-	-	-	Blood level of Hcy, B12 and folate
Ozer et al. (2006)	17	-	-	-	-	-	-	-	-	-	Blood level of Hcy, B12 and folate - \uparrow Hcy = > 14 μ mol/L - Low or normal = < 14 μ mol/L
Camicioli et al. (2009)	PD:21 HC:5	?	?	?	?	?	-	-	-	-	Blood level of Hcy, B12, creatinine and folate - \uparrow Hcy= >14 μ mol/L
Hassin-Baer et al. (2006)	28	-	-	-	-	-	-	-	-	-	Blood plasma level of Hcy: 1 st tertile (<12.5 μ mol/L), 2 nd tertile (12.5-16.7 μ mol/L)and 3 rd tertile (>16.7 μ mol/L) - Common Carotid Artery Intima-media Thickness(CCA-IMT)
Matteau et al. (2010)	-	44	?	30	?	34	?	-	-	-	- History of smoking in the past 10 years (yes/no) - Interviews
Ślawek et al. (2008)	-	20	3	14	28	16	-	7	-	-	- Interviews - MRI: WMH [Wahlund Scale]
Zoccolella et al. (2005)	24	-	-	-	-	-	-	-	-	-	Blood level of Hcy, B12 and folate - \uparrow Hcy= >14 μ mol/L
Marder et al. (1990)	-	?	-	?	-	-	-	?	-	-	- Interviews - Questionnaires
Rektor et al. (2009)	-	11	5	14	14	-	4	-	-	-	- Number of cigarettes and duration - Questionnaires and medical records - MRI - CCA-IMT, PI & RI

Legend: - (not applicable), ? (unknown or not clear); Vascular risk factors (VRF): \uparrow Hcy (Hyperhomocysteinemia), DM (Diabetes Mellitus), HCL (Hypercholesterolemia), HD (Heart Disease), HT (Hypertension), SMO (Smoking), HS (Stroke), IAA (Ischemic Attacks); VRF measures: \downarrow Hcy (Low/normal Level of Homocysteine), CCA-IMT (Common Carotid Artery Intima-media Thickness), Hcy (Homocysteine), MRI (Magnetic Resonance Imaging), PI (Pulsatility Index), RI (Resistance Index), WMH (White Matter Hyperintensity), L-dopa (levodopa); Medication: Anti-ACh (Anticholinergics), DAA (Dopamine Agonist), L-dopa (levodopa); Groups: PD (Parkinson's disease-Cognitively Normal), PDD (Parkinson's disease with Dementia), PD-MCI (Parkinson's disease with Mild Cognitive Impairment)

Table 3. Vascular Risk Factors and their Measurements

Authors	Cognitive measures	Cognitive results	Other key results
Barone et al. (2008)	<div><div>- Global Cognition: MMSE, ADAS-Cog, ADCS-CGIC</div><div>- Attention-Vigilance : CDR-Computerized Assessment System PoA tests</div><div>- Speed of information processing : CRT</div><div>- Language : D-KEFS letter fluency score</div></div>	<div><div>- BL ADAS-Cog: ↑Hcy PD group= ↓Hcy or normal PD group</div><div>- BL MMSE: ↑Hcy PD group= ↓Hcy or normal PD group</div><div>- BL dementia severity (per MMSE total scores): ↑Hcy PD group= ↓Hcy or normal PD group</div><div>- ADAS-Cog at week 24: ITT-RDO, LOCF and OC analyses: ↑Hcy- PD group treated with rivastigmine improved > ↓Hcy-PD group with placebo (p < .001)</div><div>- ADCS-CGIC at week 24: ITT-RDO and LOCF analyses: ↑Hcy- PD group treated with rivastigmine improved > ↓Hcy- PD group with placebo (p = .003); OC analysis (p < .001)</div><div>- ADCS-CGIC (% of responders) at week 24: ITT-RDO analyses: ↑Hcy PD group treated with rivastigmine > ↓Hcy PD group with placebo (p = .010)</div><div>- ADCS-CGIC (% of patients with mild, moderate or marked deterioration relative to baseline) at week 24: ITT-RDO analyses: ↑Hcy- PD group treated with rivastigmine < ↓Hcy- PD group with placebo (p = .011)</div><div>- MMSE score at week 24: ITT-RDO analyses: ↑Hcy- PD group treated with rivastigmine < ↓Hcy- PD group with placebo (p = .012)</div><div>- PoA at week 24: ITT-RDO analyses: ↑Hcy- PD group treated with rivastigmine < ↓Hcy- PD group with placebo (p = .037)</div><div>- CRT at week 24: ITT-RDO analyses: ↑Hcy- PD group treated with rivastigmine < ↓Hcy- PD group with placebo (p = .007)</div><div>- D-KEFS letter fluency score at week 24: ITT-RDO analyses: ↑Hcy- PD group treated with rivastigmine < ↓Hcy- PD group with placebo (p = .006)</div><div>- On all cognitive measures at week 24: ↓Hcy or normal PD group treated with rivastigmine = ↓Hcy or normal PD group with placebo (p = NS)</div></div>	<div><div>- BL demographics (gender; time since 1st symptoms of PD, since PD diagnosis, since 1st dementia symptoms and since PDD diagnosis; H & Y stages; UPDRS^{III} scores; L-dopa, DAA, antipsychotics, antidepressants, benzodiazepines, sedatives and hypnotic agents intake): ↑Hcy-PD group= ↓Hcy or normal PD group</div><div>- BL ADCS-ADL: ↑Hcy- PD group < ↓Hcy or normal PD group (p=.025)</div><div>- BL hallucinations: ↑Hcy- PD group > ↓Hcy or normal PD group (p=.005)</div><div>- ADCS-ADL at week 24: ITT-RDO analyses: ↑Hcy- PD group treated with rivastigmine > ↓Hcy- PD group with placebo (p = .033)</div><div>- NPI-10 score at week 24: ITT-RDO analyses: ↑Hcy- PD group treated with rivastigmine > ↓Hcy- PD group with placebo (p = .003)</div><div>- NPI-Caregiver distress at week 24: ITT-RDO analyses: ↑Hcy- PD group treated with placebo (p = NS)</div><div>- On ADCS-ADL, NPI-10 score and NPI-Caregiver distress at week 24: ↓Hcy or normal PD group treated with rivastigmine = ↓Hcy or normal PD group with placebo (p = NS)</div></div>
Alves et al. (2004)	<div><div>- Global Cognition: MMSE</div></div>	<div><div>- MMSE at BL: PD smokers= PD non-smokers</div><div>- MMSE changes (4 & 8 yrs): PD smokers= PD non-smokers (20 pack-years and more)</div></div>	<div><div>- % PD smokers < % HC smokers & DM smokers (p<.01)</div><div>- Gender: M > F in PD smokers (p<.001)</div><div>- Age at PD onset: SMO (62.4) < non-SMO (65.1) (p<.05)</div><div>- H&Y changes (4 & 8 yrs): SMO=no-SMO (p= NS)</div><div>- MADRS changes (4 & 8 yrs): SMO=no-SMO (p= NS)</div><div>- S&E changes (4 & 8 yrs): SMO=no-SMO (p= NS)</div><div>- UPDRS changes (4 & 8 yrs): SMO=no-SMO (p=NS)</div><div>- Survival rate (8 yrs): SMO=no-SMO (p=NS)</div><div>- 30 smokers still alive (38.5%)</div><div>- 59 non-smokers still alive (36.6%)</div></div>
Haugarvoll et al. (2005)	<div><div>- Global Cognition : GBS (BL), MMSE, DRS (FU), UPDRS (intellectual item)</div><div>- Episodic Memory (visual) : BVRT</div><div>- Executive Functions : Stroop</div><div>- Visual perception : B/I/O</div></div>	<div><div>- PD-D at FU : VRF (35% with PDD) = no-VRF (31% with PDD) (p= n.s.)</div><div>- Heart failure: PDD > PD (p<.05) [univariate analysis only] . This association was not found in the logistic regression controlling for age, H & Y, low MMSE, gender.</div></div>	<div><div>- Atrial fibrillation & Smoking: men > women respectively (p<.05) and (p<.001)</div><div>- Mortality: VRF (24%) > no-VRF (16.9%) (p=NS)</div><div>- Mortality: 36/171 deceased at FU (21%)</div></div>

Kandiah et al. (2009)	<ul style="list-style-type: none">- Global Cognition: MMSE	<ul style="list-style-type: none">- CD group : -2.39 points/year on MMSE- Cox proportional hazards model:- Univariate analysis: Education ($p=.003$), age ($p=.008$) and depression ($p=.043$) but not DM predicted CD- Multivariate analysis: Only (low) education predicted CD [HR=.91, 95% CI (.82-.99), $P=.047$]	<ul style="list-style-type: none">- Severity of motor symptoms (UPDRS) and H & Y stage did not influence CD.
Levy et al. (2002); Stern et al. (1992)	<ul style="list-style-type: none">- Orientation: Items from MMSE, BNT, BDAE (some subtests)- Episodic memory (verbal): SRT- Episodic memory (visual): BVRT- Executive functions: Similarities (WAIS-R); DRS (Identities and Oddities)- Visual perception: BVRT-Matching part	<ul style="list-style-type: none">- Current smoking & risk for PDD: (RR 4.5; 95% CI, 1.2-16.4; $P=.02$)- Past smoking & risk for PDD: (RR 2.0; 95% CI, 1.0-3.9$p=.05$)- Smoking (cessation): < 8 yr before PD = ↑ Risk for PDD (RR 2.3; 95% CI, 1.1-4.9; $P=.03$)- Smoking: ↑ pack-year ≠ ↑ RR for PDD- Smoking: ↑ smoking duration ≠ ↑ RR for PDD- Alcohol, DM & HT ≠ development of PDD	<ul style="list-style-type: none">- BL Age: PDD > PD ($p<.05$)- BL Education: PDD < PD ($p<.05$)- BL motor signs (UPDRS): PDD > PD ($p<.05$)- FU: ApoE-ε4 ≠ Incident PDD ($P=NS$)
O'Suilleabhain et al. (2004, 2006)	<ul style="list-style-type: none">- Global cognition: MMSE- Attention: Digit span (WAIS-III), (COWAT)- Language: Verbal Fluency Tests- Episodic memory (verbal): HVLT-Revised- Episodic memory (visual): ROCF (immediate & delayed recall)- Executive functions: Stroop- Construction Praxis: Block Design (WAIS-III), ROCF (copy)	<ul style="list-style-type: none">- BASELINE (2004)- Cognition (averaged Z scores of 14 tests) worse in Hcy >14 μmol/L than in Hcy < 14 μmol/L ($p<.01$)- Cognitive results (analysis of variance):- PD with Hcy>14 μmol/L < PD with Hcy < 14 μmol/L only on Block design, animal fluency, ROCF-copy ($p<.05$)- FOLLOW-UP (2006)- Cognitive results (decline): ↑Hcy = nHcy (NS) on all cognitive measures except- for ROCF-immediate recall on which PD with ↑Hcy declined significantly compared to 2004 ($p=.035$) whereas nHcy did not.	<ul style="list-style-type: none">- BL&FU- Age: ↑Hcy > nHcy ($p=.06$)- L-Dopa dose: ↑Hcy > nHcy ($p=.003$)- BL (2004)- Age ↔ Hcy ($p=.28$, $p=.006$)- Mood: ↑Hcy [>14 μmol/L] (worst) < nHcy ($p=.02$)- Creatinine ↔ Hcy ($r=.32$, $p=.001$)- Higher L-dopa dose ↔ higher Hcy level ($r=.35$, $p<.01$)- Hcy levels: L-dopa users > non-users ($p=.01$)- Plasma L-dopa ↔ Hcy ($r=.42$, $p<.002$)- MTHFR: Hcy level the same with or without T alleles- Plasma B12 ↔ Hcy- $r=-.34$, $p=.04$ among L-Dopa non-users- $r=-.04$, $p=NS$ among L-Dopa users- UPDRS ↔ Hcy >14 μmol/L ($p=.20$)
Rodriguez-Oroz et al. (2009)	<ul style="list-style-type: none">- Global Cognition: MMSE, BDS- Episodic Memory: CERAD Word List, FCSRT, Copy & delayed recall of 2 simple figures- Language: BNT; Verbal Fluency Tests- Attention: Digit Span (Forward and Backwards)- Executive functions : Stroop, TMT-A & B, Raven Progressive Matrices	<ul style="list-style-type: none">- Hcy ≠ predict cognitive status ($p=.403$) (multinomial logistic regression)- Cognitive tests results ≠ Hcy levels (all correlation: $p=NS$)- Cognitive status ≠ polymorphisms studied ($p=NS$)- Genes (variants) = MTHFR677T (CC, CT, TT), MTHFRA1298C (AA, AC, CC), , MTRA2756G (AA, AG, GG), & CBS844ins68(IL, ID, DD)- WMH (per the Wahlund scale) : PD-CN = PD-MCI = PDD ($p=NS$)	<ul style="list-style-type: none">- Age : PDD > HC & PD-CN ($p=.0001$) & PD-MCI ($p=.02$)- GDS : PDD > PD-CN ($p=.001$)- GDS : PD-MCI > PD-CN ($p=.04$)- Hcy levels ≠ depression ($p=NS$)- Hcy: all PD patients > HC ($p=.0001$)- HC : 8.6 μmol/L- PD-CN : 14.9 μmol/L- PD-MCI : 15.1 μmol/L- PDD : 15.4 μmol/L

Camicioli et al. (2009)	<div><div><div><div><div>- Global cognition: MMSE, DRS</div><div>- Language: NART</div><div>- Episodic memory: BDS Orientation-Memory-Concentration</div><div>- Construction praxis: CDT</div><div>- Executive functions: FAB</div><div>- Visuconstruction praxis: CDT</div></div></div><div><div><div><div>- Hcy, B12 and folate levels:</div><div>- NO ↔ with cognitive results per the DRS (p= NS)</div></div></div></div><div><div><div><div>- GDS: PD > HC (p=.001)</div><div>- No ↔ of depressive symptoms per the GDS with Hcy, B12 and folate levels.</div><div>- Hcy: PD (13.6 μmol/L) > HC (10.5 μmol/L) (p<.0005)</div><div>- In PD with L-dopa: no ↔ with L-dopa duration and L-dopa dose</div><div>- No ↔ between Hcy and B12.</div><div>- Hcy level ↔ folate (r=.31, p=.035)</div><div>- B12: PD (299.0 pmol/L) < HC (379.0 pmol/L) (p=.01)</div><div>- Use of vitamin B12 ↔ lower Hcy (p=.02 for PD & HC)</div><div>- Logistic regression model:</div><div>- ↑B12 ↔ lower risk of dyskinesias (RR 0.99, 95% CI: 0.983-0.999, p=.027)</div><div>- MTHFR genotype:</div><div>- ANOVA (PD versus HC):</div><div>- Significant group difference for MTHFR 677 genotype and B12 use (F=13.8, p < .0005) but only significant association for B12 use (F=21.5, p < .0005).</div><div>- Significant interaction between MTHFR genotype and B12 (F= 5.2, p=.02).</div></div></div></div></div></div>
Hassin-Baer et al. (2006)	<div><div><div><div><div>- Global Cognition: MMSE</div><div>- Attention: Digit Span (Forward and Backwards)</div><div>- Episodic Memory (verbal): RAVLT</div><div>- Language: Verbal Fluency Tests</div><div>- Executive functions : TMT A-B, FAB</div></div></div><div><div><div><div>- One-way analysis Kruskal-Wallis test of variance:</div><div>- All cognitive tests: No differences between the 1st, 2nd and 3rd tertile of Hcy levels.</div></div></div></div><div><div><div><div>- Correlation between L-dopa treatment duration and Hcy level (p=.036)</div><div>- No effect of L-dopa dose on Hcy levels.</div><div>- No correlation between vascular comorbidity (coronary heart disease or with history of cerebrovascular disease, such as stroke or TIA) and Hcy levels.</div></div></div></div></div></div>
Matteau et al. (2010)	<div><div><div><div><div>- Global Cognition: MMSE</div></div></div><div><div><div><div>- PD duration ↔ MMSE (r= -.22; p=.02)</div><div>- PD-VRF < PD-noVRF on the MMSE total Z score F(2,115)=5.58, p=.005, d=.3</div></div></div></div><div><div><div><div>- VRF (except HD) ≠ Cognitive status PDD > PD-CN (p<.01); HD</div><div>- HD: weak predictive factor of dementia</div><div>- HD ↔ MMSE, RAVLT, VFT all p<.05</div></div></div></div></div></div>
Slawek et al. (2008)	<div><div><div><div><div>- Global cognition: MMSE</div><div>- Intelligence: WBIS</div><div>- Language: Verbal Fluency Test (Animals)</div><div>- Episodic memory: RAVLT, DCS</div><div>- Executive functions: Tower of Toronto</div></div></div><div><div><div><div>- VRF (except HD) ≠ Cognitive status PDD > PD-CN (p<.01); HD</div><div>- HD: weak predictive factor of dementia</div><div>- HD ↔ MMSE, RAVLT, VFT all p<.05</div></div></div></div></div></div>
Zoccolella et al. (2005)	<div><div><div><div><div>- Global cognition: MMSE</div><div>- Executive functions: FAB</div></div></div><div><div><div><div>- Hcy : PD-Cogl (21.2 μmol/L) > PD-CN (15.8 μmol/L) (p=.001)</div><div>- Most common CI in PD-CI: memory impairment (n=12), apraxia (n=8), dementia per DSM-III-R (n=5)</div></div></div><div><div><div><div>- Logistic regression</div><div>- Risk of Cogl ↑ with ↑ Hcy (continuous variable): OR=19.1 (95% CI: 1.5- 241.4; p=.02)</div><div>- Risk of Cogl ↑ in the Hcy highest quartile compared to the lowest quartile: (OR=19.0; 95%CI: 1.0-346.2, p=.004) after adjustment for age, sex, B12 and folate status</div></div></div></div></div></div></div>

Marder et al. (1990)	- Global cognition: mMMS	- SMO: PDD = PDnD (p=NS); Logistic regression: OR= 1.62 (95%CI: .484-4.127) - ALC (beer): Logistic regression: OR= 2.64 (95%CI: .712-7.073) - HT(antihypertensive drugs): PDD = PDnD (p=NS)	- Age: PD - 1st degree regressi - Amateur .614-7.8
Rektor et al. (2009)	- Global cognition: MMSE - Orientation: BTOT - Language: Verbal Fluency Test (Category) - Episodic memory: Word List I-II (WMS-III) - Construction praxis: CDT	- Cognitive tests results - ↑ CCA-IMT ↔ Cognitive tests results (<i>p</i>< .05): - <i>MMSE</i> (<i>r</i> = -.44, <i>p</i> =.004), <i>CDT</i> (<i>r</i> = -.42, <i>p</i> =.007), <i>MMSE+ Clock</i> (<i>r</i> =-.49, <i>p</i> =.001), <i>BTOT</i> (<i>r</i> = .42, <i>p</i> =.006), <i>VFT</i> (<i>r</i> = -.32, <i>p</i> =.043), <i>WMS-III (recognition-word list II)</i> (<i>r</i> =-.33, <i>p</i> =.037) - RI ↔ Cognitive tests results (<i>p</i><.05) - <i>BTOT</i> (<i>r</i> = .32, <i>p</i> =.039) - PI ↔ Cognitive tests results (<i>p</i>≤.05) - <i>CDT</i> (<i>r</i> = -.35, <i>p</i> =.023), <i>BTOT</i> (<i>r</i> = .56, <i>p</i> =.0001), <i>VFT</i> (<i>r</i> =-.348, <i>p</i> =.05), <i>WMS-III (delayed recall-word list II)</i> (<i>r</i> =-.42, <i>p</i> =.007,), <i>WMS- III (recognition-word list II)</i> (<i>r</i> =-.35, <i>p</i> =.025) - Multiple regression analysis: IMT ↔ with MMSE and MMSE+ Clock & PI ↔ with BTOT and WMS-III (<i>recognition-word list II</i>)	- MRI: n= 10,000m - Atheros haemod - Multipl stage, IA

? =unknown or unclear /NS = Not Significant
Legend: ↑ (Increase), ↔ (Association), ADAS-Cog (Alzheimer’s Disease Assessment Scale- Cognition), ADCS-ADL (A Study-Activities of Daily Living), ADCS-CGIC (Alzheimer’s Disease Cooperative Study-Clinician’s Global Impression Scale), BFR (Benton Face Recognition), BJLO (Benton Judgment of Line Orientation), BL (Baseline), BNT (Boston Naming Orientation Test), BVRT (Benton Visual Retention Test), CCA-IMT (Common Carotid Artery Intima-Media Thickness) (Cognitive Drug Research), CDT (Clock Drawing Test), CI (Confidence Interval), CogI (Cognitive Impairment), COWA (Cognitive Word Association Test), CRT (Choice Reaction Time), DA (Dopamine), D-KEFS (Delis-Kaplan Executive Fonction System), DRG (Dementia Rating Scale), dx (Diagnosis), EBMT (East Boston Memory Test), FAB (Frontal Assessment Battery), FCSRT (Frontal C Stroop Test of Buschke), FU (Follow-up), GBS (Gottfried-Brane-Steen scale), GDS (Geriatric Depression Scale), H & Y (Hoehn and Yahr), HT (hypertension), HVLIT (Hopkins Verbal Learning Test), IADL (Instrumental Activities of Daily Living), IIT-RDO (Intra-Individual Test of Recall-Delay Out), LOCF (Last Observation Carried Forward), MC (Multiple Centers), MMSE (Mini-Mental State Examination), nH (no hypertension), VRF (No Vascular Risk Factors), NPI (Neuropsychiatric Inventory), NSAID (Nonsteroidal Anti-Inflammatory Drug), OR (Odds Ratio), PD-CN(Parkinson’s Disease – Cognitively Normal), PDD (Parkinson’s Disease with Dementia), PD-MCI (Parkinson’s Mild Cognitive Impairment), PDnD (Parkinson’s disease, no dementia), PoA (Power of Attention tests), PI (Pulsatility Index), RAVLT (Rey-Osterrieth Complex Figure Test), RI (Resistance Index), ROCF (Rey-Osterrieth Complex Figure), RR (Risk Ratio), S&E (Schwab and England score), STMS (Short Test of Mental Status), sx (Symptoms), TMT (Trail Making Test), UPDRS (Unified Parkinson’s Disease rating scale), Task), VRF (Vascular Risk Factors), WBIS (Wechsler-Bellevue Intelligence Scale), WMH (White Matter Hyperintensities), WMH (White Matter Hyperintensities Scale, 3rd version), WCST (Wisconsin Card Sorting Test), WMH (White Matter Hyperintensities), WS (Wahlund Scale)

Table 4. Cognitive Measures, Cognitive Results and Other Key Results

3.6.8 Construction praxis

Construction praxis was assessed in 4 studies using the Clock Drawing Test (CDT) (n=3 studies), the Block Design of the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) and the copy part of the ROCF. Only 1/4 studies reported a significant association between the presence of VRF and a decline in the construction praxis. O'Suilleabhain et al. (2004; 2006) found a significantly worse performance on Block Design (WAIS-III) and on ROCF-copy in the PD group with Hcy > 14 µmol/L compared to PD with Hcy < 14 µmol/L at baseline, but not at 2-year follow-up.

Ozer et al. (2006) didn't find significant differences on the CDT score between PD ≥ 14 µmol/L, PD < 14 µmol/L and healthy controls. Camicioli et al. (2009) didn't report results of specific analyses concerning the CDT. In addition, CDT was significantly associated with an increase of intimomedial thickness and of the pulsatility index, but not with the presence of smoking, HT, DM, ischemic HD and stroke (Rektor et al., 2009).

3.6.9 Orientation

Orientation was assessed in 2 studies using the Benton Temporal Orientation Test (BTOT) (1 study) and some MMSE items (1 study). Positive correlations between the BTOT and the increase of intimomedial thickness, the pulsatility index and the resistance index were found, but there was no correlation with smoking, HT, DM, ischemic HD and stroke (Rektor et al., 2009). Levy et al. (2002) didn't report results on the MMSE-orientation items.

3.6.10 Speed of information processing

Speed of information processing was assessed in only one study with the Choice Reaction Time (CRT) test. The R-DB-PC study of Barone et al. (2008) found that ↑Hcy patients treated with rivastigmine had a significant improvement on the CRT after 24 weeks compared to ↑Hcy-placebo-treated patients, and this improvement wasn't present in the < 14 µmol/L group.

4. Conclusion

The main objective of this review was to determine whether there is a relationship between VRF and cognition in PD or not. Consequently, a thorough search in several relevant databases was conducted, and 18 studies were found. After a comprehensive analysis of the articles content, a relationship was evidenced between cognition and ↑Hcy, but the link between heart disease, smoking and cognition was more controversial. There was no evidence of any relationship between cognition and diabetes mellitus, hypertension, alcohol intake, stroke history/transient ischemic attack and hypercholesterolemia.

4.1 Homocysteine and cognition

Hyperhomocysteinemia in PD was associated with worse cognition and/or dementia in 6/9 studies of this review; 3/9 studies found no association. This finding is partly supported by the results of a previous review of 16 articles by Zoccolella et al. (2010) who reported significant associations in 9 publications investigating cognition or dementia in relationship with ↑Hcy. Nine out of 16 studies of Zoccolella and colleagues overlapped some articles

included in the current review. However, the inclusion criteria of the current review were more rigorous, and excluded published abstracts of conference presentations. Furthermore, the current review also collected more demographic and clinical data on PD patients and controls, and reported results in a more detailed fashion, hence allowing easier comparisons and exploration of possible interactions or co-occurrence between VRF. Nevertheless, the relationship between cognition/dementia and ↑Hcy remained relatively consistent.

Some of the divergent findings in the global cognitive outcomes of the 9 studies that investigated Hcy may be explained by several factors. For instance, in all these studies, those with greater sample size and using a longitudinal design were more likely to find a significant association compared to the studies that didn't find a significant association. In brief, studies that found significant associations possibly presented a more robust design, greater statistical power and also possibly a higher dosage of L-dopa. Among the 3 studies that didn't find an association with Hcy and cognition, one didn't clearly report medication dosages. Other possible explanations involve the use of different technologies to measure Hcy levels (high performance liquid chromatography with fluorescence detection, fluorescence polarization immunoassay, chemiluminescent enzyme immunoassay) and the measurement of Hcy levels under different fasting conditions (food and drugs).

Interestingly, the Hcy studies demonstrated that ↑Hcy may affect episodic memory (O'Suilleabhain et al., 2004, 2006; Ozer et al., 2006), executive functions (Ozer et al., 2006), language (Barone et al., 2008; O'Suilleabhain et al., 2004, 2006), attention/vigilance (Barone et al., 2008), construction praxis (O'Suilleabhain et al., 2004, 2006) and speed of information processing (Barone et al., 2008). This could reflect a vascular contribution to cognitive impairment since executive functions, attention and some aspects of episodic memory are linked to frontal-subcortical loops (Sachdev et al., 2005). Indeed similar results were found in studies performed in elderly with VRF, some even found poorer performance with ↑Hcy for specific cognitive domains like episodic memory (Morris et al., 2001), executive functions (Duthie et al., 2002) and attention (Duthie et al., 2002). However, this cognitive profile is prominently found in PD patients with cognitive impairment (without VRF), since the alteration of the frontal-striatal system could cause a similar executive dysfunction (Zgaljardic et al., 2003). Hence, it could be hypothesized that: 1) ↑Hcy amplifies the severity of the executive impairment already present in PD patients; and/or 2) that ↑Hcy increases the susceptibility of some cerebral regions to vascular impairment (i.e. ischemic lesions in these specific regions); and/or 3) that ↑Hcy accelerates the neurodegenerative process of PD in some aspects, because of its acknowledged neurotoxicity (Sachdev, 2005). Nonetheless, further research is required to clarify these hypotheses.

4.1.1 What could explain the link between Hcy and cognition?

Elevated Hcy is associated with brain atrophy by several vascular mechanisms (for a review on the question, see Sachdev, 2005) such as promoting endothelial cell injury (formation of atherosclerosis in the blood vessel walls and reduced thrombo-resistance), increasing platelet aggregation (by increasing thromboxane A₂ synthesis and decreasing prostacyclin), affecting factors of the clotting cycle (and inhibition of the natural anticoagulants), and favors the adhesion of platelets to the endothelium. Hence, these results may support a possible vascular contribution to cognitive impairment by ↑Hcy. As mentioned in section 3.4.1, L-dopa intake in PD patients induces increased levels of Hcy (Kuhn et al., 1998; Müller

et al., 1999; Rogers et al., 2003; Yasui et al., 2000) because L-dopa breakdown interferes with Hcy metabolism. Since Hcy also has been associated with hypertrophy of the intima-media complex of the carotid artery, a marker of atherosclerotic disease (Megnien et al., 1998), L-dopa-induced ↑Hcy may promote systemic atherosclerosis processes, thus compromising vascular health. This is supported by the findings of Nakaso et al. (2003) who reported that patients treated with L-dopa for longer duration had increased hypertrophic changes in the intima-media complex of the carotid artery, and that ↑Hcy promoted by both longer L-dopa treatment and MTHFR T/T genotype may amplify atherosclerotic processes.

4.1.2 Neurotoxicity of homocysteine

In the current review, the study conducted by Barone et al. (2008) brought indirect support for a neurotoxic effect of Hcy on brains cells. As mentioned above, ↑Hcy causes increased oxidative stress, excitotoxicity, promotes cellular apoptosis and accumulation of amyloid β -peptide and abnormal tau phosphorylation. The brain is particularly vulnerable to ↑Hcy, because it lacks two major Hcy metabolic pathways (via methionine synthase and via cystathionine- β -synthase)(Finkelstein, 1998). The R-DB-PC study of Barone et al. (2008) successfully demonstrated that global cognitive function, verbal fluency, attention, and speed of information processing of hyperhomocysteinemic PD patients benefited from rivastigmine treatment. These results may support the hypothesis of the contribution of a cholinergic system imbalance in cognitive impairment and dementia in PD. Indeed, rivastigmine inhibits acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) (Darreh-Shori et al., 2002), two enzymes that catalyze the hydrolysis of acetylcholine (ACh) in neurons (Lane et al., 2006). Hyperhomocysteinemia could be deleterious to the ACh system of PDD because a metabolite of homocysteine (*homocysteine thiolactone*) is known to increase the enzymatic activity of BuChE (Darvesh et al., 2007). Since the BuChE highest activity is reported in deep gray and white matter brain regions, hyperhomocysteinemia may be linked to subcortical atrophy and white matter lesions (Darvesh et al., 2007; Sachdev et al., 2005). Apart from the compensation for ACh deficiencies, another hypothesis for the benefit of rivastigmine treatment could be that rivastigmine may reduce inflammation and oxidative stress in neurons (Schulz et al., 2002; Tanaka et al., 1995). These pathological phenomena are promoted by ↑Hcy (Sachdev et al., 2005) and could be involved in PDD. Nevertheless, the underlying mechanisms of rivastigmine treatment effects on cognition in hyperhomocysteinemic patients are still hypothetical (Barone et al., 2008).

4.2 Smoking and cognition in PD

The question of whether smoking is a protective factor for PD or a factor promoting cognitive impairment and dementia is very controversial. A significant relationship between cognition and smoking in PD was found in 3/8 studies of this review: a higher risk for dementia in current smokers (Levy et al., 2006), and a worse performance on a global cognitive measure in patients with history of smoking (indirectly in Matteau et al., 2010; and directly in Weisskopf et al., 2007). Nevertheless, the data extracted from the 8 articles were conflicting since 5/8 studies didn't find a significant association between cognition and smoking in PD. However, most of these 5 studies only reported smoking as present or not in the sample. Consequently, comprehensive analyses between different smoking status and cognitive results were not conducted. In fact, Haugarvoll et al. (2005), Rektor et al. (2009)

and Slawek et al. (2008) didn't report results specific to smoking. Moreover, the number of PD smokers in the samples was very small, thus making it difficult to draw any conclusion on the definitive impact of smoking on cognition in PD. It could be argued that studies that found significant associations had a larger sample size of smokers and thus more statistical power. In addition, when specified, the number of current smokers compared to past smokers was relatively small. Although some studies assessed smoking in a more detailed fashion, cognition was only assessed with brief global measures that could potentially mask effects on specific cognitive domains. Hence, it is justified to doubt if cognitive deficits, when found in association with smoking, were present at the time of diagnosis or reflected a faster decline after PD onset. Nevertheless, an early study evaluating the risk of dementia in PD smokers compared to non smokers (Ebmeier et al., 1990) found that the odds ratio for dementia in smokers was 4.0 (95% CI:1.4 -12.0) compared to non smokers, which clearly indicates a risk for cognitive deterioration in PD smokers.

The controversy regarding the association between smoking and greater cognitive decline in PD patients stems from the fact that tobacco use has been quite consistently reported as a dose-dependent protective factor for PD development in several studies as evidenced in the pooled analysis of Ritz et al. (2007). Although the current review couldn't draw definitive conclusions on smoking as a VRF for cognitive decline in PD, some hypotheses can be made over the conflicting results. Animal studies hypothesized that nicotine delivered through cigarette smoke may exert a protective effect on dopaminergic (DA) neurons in the substantia nigra, thus enhancing the survival rate of animals. In fact, Parain et al. (2003) examined the effects of cigarette smoke and nicotine in an animal model of PD provoked by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication in mice. They found that the loss of DA neurons in the substantia nigra was significantly less severe in the group treated with injections of nicotine and in the group with low exposure to cigarette smoke, compared to the groups treated with placebo and highly exposed to cigarette smoke.

Moreover, the study of Park et al. (2007) with microglia cultures demonstrated that nicotine had a neuroprotective effect on DA neurons due to an anti-inflammatory action. Supporting the results of animal studies, Kelton et al. (2000) reported improvements in reaction time, central processing speed and tracking in 15 non-demented PD patients after they received an acute administration of nicotine (phase I). Several motor measures also improved after chronic administration of nicotine patches (phase II), thus reinforcing the aforementioned hypothesis. This is particularly interesting for PD, since alterations of the nicotinic binding sites in the pars compacta of the substantia nigra were associated with PD (as well as in AD and in Lewy body disease) (Perry et al., 1995). In fact, abnormalities of the nicotinic receptors may precede DA neurodegeneration.

On the other side, while nicotine may protect against nigral neuronal losses, side effects from the other compounds of cigarette smoke may be deleterious for the vascular system and for brain cells health even in non PD elderly. A diminution of gray matter density in the posterior cingulate cortex, the precuneus, the right thalamus and the frontal cortex were found in elderly smokers (otherwise healthy) compared to non-smokers. These cerebral regions are associated with incipient AD (Almeida et al., 2008). Some neuroimaging studies associated smoking with increased cerebral infarcts, white matter hyperintensities, subcortical atrophies and elevated amyloid plaques (Swan & Lessov-Schlaggar, 2007; Tyas et al., 2003). Furthermore, some studies conducted in non-demented elderly reported that

smoking increased difficulties in psychomotor and information processing speed (Hill, 1989; Kalmijn et al., 2002), verbal learning, cognitive flexibility (Kalmijn et al., 2002), distracters inhibition and global executive functions (Paul et al., 2006; Razani et al., 2004). However, some authors didn't find any deleterious effect of smoking on cognitive measures (Schinka et al., 2002). These findings highlight the controversy regarding the impact of cigarette smoking on cognition. Nonetheless, the results of the current review cannot draw a specific cognitive profile in PD associated with smoking as a VRF, because significant effects were only reported on global cognitive measures. In fact it is possible that cigarette smoking – especially nicotine in cigarette smoke – could affect PD brains differently than healthy elderly, probably because of PD-related changes.

4.3 Heart disease and cognition in PD

The data of the current review associated the presence of HD in PD with dementia (Haugarvoll et al., 2005; Slawek et al., 2008), and impairment in episodic memory and language (Slawek et al., 2008). However, these associations were weak and controversial, since another study did not report any association (Rektor et al., 2009). Yet the association between HD and cognition in PD is at least partly supported by the literature in non-PD elderly. For instance, Ylikoski et al. (2000) reported that non-PD elderly with heart failure and showing white matter changes and central atrophy had significantly worse cognitive performance in tests measuring visuoconstruction, attention and cognitive flexibility compared to healthy individuals. Interestingly, several studies strongly associated ↑Hcy with a higher risk of HD in healthy individuals. For instance, a meta-analysis by Wald et al. (2002) evidenced a causal relationship between Hcy levels and ischemic HD and found that lowering Hcy levels from current level by 3μmol/L could reduce the risk of ischemic HD by 11% to 20%. Nonetheless, none of the articles investigating Hcy in this review reported the cardiac health condition of the ↑Hcy patients and none of the studies reporting heart diseases assessed Hcy levels, so this relationship wasn't reported in the 9 articles.

4.4 Diabetes mellitus, hypertension, hypercholesterolemia, alcohol and cognition in PD

None of the studies of this review reported a significant association between DM, HT and HCL and cognition in PD. However, in most cases, these VRF were considered only as secondary variables and the potential relations with cognition were not always thoroughly assessed. In addition, these results don't reflect those obtained in non-PD populations, because several studies associated type 2 DM with cognitive impairment. A literature review showed that type 2 DM is cross-sectionally associated with cognitive impairment in healthy elderly and is considered as a risk factor for both vascular dementia and AD in several studies (Stewart & Liolitsa, 1999). Moreover, higher risk of poor performance on verbal episodic memory and concept formation with longer DM duration was demonstrated in a large prospective cohort of non-PD individuals with DM followed during nearly 30 years (Elias et al., 1997).

A possible explanation for the difficulty to draw specific conclusions regarding the presence of HT, DM and HCL in PD and their impact on cognition could be that some studies found inverse associations with these VRF and the risk for PD. In fact, a significant inverse relation/lower odds ratio for PD was shown in individuals with HT (Herishanu et al., 2001;

Miyake et al., 2010; Scigliano et al., 2006), DM (Herishanu et al., 2001; Miyake et al., 2010; Scigliano et al., 2006) and HCL (Miyake et al., 2010; Scigliano et al., 2006). The study of Scigliano et al. (2006) suggested that the reduced risk for vascular disorders in untreated PD patients could stem from a reduced autonomic activity in PD. While sympathetic hyperactivity is known to exacerbate high blood pressure, diabetes and dyslipidemia, PD patients present with cardiac sympathetic denervation and parasympathetic dysfunction (Buob et al., 2010; Shibata et al., 2009), thus possibly reducing HT and other VRF related to it. In addition, the reduction in sympathetic activity may be relevant for postural hypotension reported in 70% of PD patients (Appenzeller & Goss, 1971; Shindo et al., 2003). The fact that patients were untreated in the study of Scigliano et al. (2006) could be a key factor since L-dopa-treated patients are more susceptible to have higher Hcy levels (see section 3.4.1), they are also at an increased risk for cerebrovascular and cardiovascular disorders. Yet, Jellinger (2003) found that the frequency of brain lesions associated with vascular disease such as white matter lesions, ischemic infarcts, hemorrhages and lacunes, was higher in PD patients compared to controls, but more severe ischemic and hemorrhagic strokes often leading to death were less frequent in PD patients. The findings of Jellinger thus mitigate the impact of cerebrovascular lesions in PD patients.

4.5 Limitations of the reviewed articles

The studies included in the review presented several limitations. There was a small number of studies for some VRF such as DM, HCL, HT, HD, SH/TIA and as a consequence, there was a lack of analyses on these variables in link with cognitive measures. For instance, although HT didn't seem associated with cognition in 6/9 studies, 3/9 did not report if there was any association or not, thus suggesting that these analyses were not even realized, probably because these VRF weren't the main focus in these studies. Moreover, it is rather difficult to draw a conclusion regarding the impact of some VRF such as SH, TIA, alcohol intake and HCL because only a few studies assessed their links with cognition. As explained previously, PD patients are less susceptible than controls to be diagnosed with HT, DM and HCL, thus making it difficult to perform a comprehensive assessment of the relation between these VRF, cognitive impairment and PDD.

The cross-sectional design of the studies could also have influenced the cognitive profile of PD patients with and without VRF. For instance, two studies with a longitudinal component (Barone et al., 2004; O'Suilleabhain et al., 2004; 2006) found a significant association with elevated Hcy and worse cognitive performance, but inconsistencies were found in the case-control studies. Thus, an important limitation of the review data concerns the lack of longitudinal and cohort studies on most VRF.

While most studies used comparable diagnostic criteria (see Table 2), a considerable number of studies reported severe exclusion criteria for PD participants, such as the exclusion of cognitively impaired or demented patients (see Table 1). Since demented and cognitively impaired PD patients were systematically excluded in 7 studies, it is possible that an association between VRF and cognition was missed in these particular studies.

Several studies (n=11) didn't report education levels of the participants, and this may have had an impact on cognitive evaluation. Education is an important variable to consider when cognition is assessed because it is strongly correlated with cognitive performance on

neuropsychological tests, and this is the reason why good standardized cognitive tests are normalized according to age and education (Lezak et al., 2004). For the reasons stated above, it is delicate to compare results of patients with low-levels of education with those of patients with higher levels of education as Weisskopf et al. (2007) and Rodriguez-Oroz et al. (2009) did in their respective study.

Only a few studies reported the use of magnetic resonance imaging (MRI) to correlate the cognitive deficits with objective brain changes and lesions. Apart from plasma measures of Hcy, the only biological measures used in the 18 articles that could without a doubt confirm a vascular disease or impairment were the measures of intima-media thickness of the common carotid artery, as well as the pulsatility and resistance index in the studies of Rektor et al. (2009) and Hassin-Baer et al. (2006).

Another important point to consider is the fact that the treatment of vascular conditions such as HT with antihypertensive medications could have mitigated the effects of some VRF, thus creating some kind of “false” at risk groups. It is particularly hard to estimate the consequences of such an effect, because most studies only reported PD-related drugs, and not the VRF treatment. Conversely, some medications such as beta-blockers, administered to control HT, are known to have deleterious effects on cognition (Gliebus and Lippa, 2007). Unfortunately this is also true for benzodiazepines (Kleykamp et al., 2010) often prescribed in PD as a muscle relaxant. Therefore it would be a good idea in the future to include information regarding medications in studies investigating the relationship between VRF and cognition in PD.

Finally, the current review had specific inclusion criteria for the articles and thus, studies that didn't report cognitive measures were not selected. However, other kinds of studies may bring some support to the effect of vascular disease and VRF on the clinical course of PD. For instance, Papapetropoulos et al. (2004) studied the impact of HT, DM, ischemic HD and stroke in late-onset PD patients and found that H&Y stages were significantly higher in patients with stroke, ischemic HD and DM compared to those without those VRF, thus suggesting some impact of VRF on disease severity and mechanisms.

4.6 Recommendations for future studies

Considering the outcomes of this review, some recommendations to improve research in this area can be formulated. Since the current review showed important inconsistencies in the neuropsychological assessment of PD patients, the development of a standardized and comprehensive assessment of cognition especially adapted for PD is mandatory. In fact, apart from the study of Weisskopf et al. (2007) that reported no changes in cognitive results after removing the results of one test that could be affected by bradykinesia, no study mentioned the use of motor controls for the neuropsychological assessment. Although some tests didn't have a motor component, others, such as the CDT and ROCF, did. Since motor impairment is a prominent feature of PD, obtaining pure cognitive measures can be challenging in tests requiring motor manipulations.

In addition, studies assessing the impact of the interaction of several VRF (such as ↑Hcy and HD; ↑Hcy and smoking) on cognition should also be performed as well as studies comparing the VRF and cognitive functions in *de novo* untreated patients versus patients treated with L-dopa (e.g. for 5, 10 and 15 years). In all these studies, structural and

functional imaging data shall be provided in order to perform correlations with the cognitive and clinical measurements.

Finally, future studies shall investigate indirectly the role of VRF in cognition by evaluating the impact of some VRF treatment like nicotine patch or antihypertensive/anti-HCL medication on the cognitive functions in PD patients.

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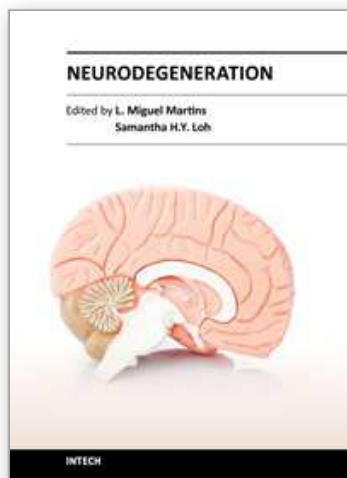
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Currently, the human population is on a collision course for a social and economic burden. As a consequence of changing demographics and an increase in human individuals over the age of 60, age-related neurodegenerative disorders are likely to become more prevalent. It is therefore essential to increase our understanding of such neurodegenerative disorders in order to be more pro-active in managing these diseases processes. The focus of this book is to provide a snapshot of recent advancements in the understanding of basic biological processes that modulate the onset and progression of neurodegenerative processes. This is tackled at the molecular, cellular and whole organism level. We hope that some of the recent discoveries outlined in this book will help to better define the basic biological mechanisms behind neurodegenerative processes and, in the long term, help in the development of novel therapeutic approaches.

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