REVIEW

The heterogeneity of cognitive symptoms in Parkinson's disease: a meta-analysis

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ABSTRACT

Several studies have reported heterogeneity in cognitive symptoms associated with specific characteristics of patients with Parkinson's disease (PD). Indeed, researchers have characterised subtypes of patients suffering from PD according to various criteria. Those most frequently used are the type of predominant motor symptoms (tremors or non-tremor symptoms), age at onset and presence of depression. Some characteristics, like the predominant motor subtypes, as well as the presence of depression, are more widely used to categorise cognitive differences between patients. The goal of this study was to analyse the impact of the type of predominant motor symptoms and depression on cognition in PD. A meta-analysis of 27 studies (from 1989 to 2012) was carried out to calculate the average effect size of these factors on the most often used cognitive test during those past years to evaluate cognitive skills, the Mini-Mental State Examination. The studies analysed showed significant mean weighted effect sizes on cognition for the type of motor symptoms (d=0.42; 95% CI 0.30 to 0.54) and for depression (d=0.52; 95% CI 0.38 to 0.66). These results suggested that PD participants with non-tremor predominant motor symptoms or with depression had more or more severe cognitive impairments. Identification of different subtypes in PD is important for a better understanding of the cognitive symptoms associated with this disease. Better knowing the impact of different features of PD subgroups could help to design more appropriate treatments for patients with PD.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterised principally by motor symptoms such as hypokinesia, bradykinesia, rigidity, tremors and postural instability.[1] PD may also cause non-motor symptoms including sleep disorders, depression and cognitive deterioration that are responsible for a significant reduction in quality of life.[2 3] When the cognitive deterioration is severe, it may result in the development of dementia in patients with PD. Prevalence of dementia in PD varies greatly across studies (from 21% to 81%).[4] However, many patients with PD but without dementia also have cognitive deficits. These deficits include executive dysfunctions in inhibition, mental flexibility, working memory, learning and planning,[1 5] which may have a significant impact on patient management and contribute to caregiver distress since executive dysfunctions may interfere with social and occupational functioning.[6] Recent studies have shown that between 20% and 40% of individuals with PD have one or more cognitive domains severely impaired and are considered to have mild cognitive impairment (MCI).[7 8]

However, it is worth noting that cognitive impairments are not observed in all individuals with PD. Some studies have reported heterogeneity in PD with regard to the presence or absence of different cognitive deficits (eg, language, visuo-spatial and memory deficits) and their severity, suggesting the existence of distinct subgroups of patients.[9 10] This heterogeneity in cognition has been associated with many factors such as dominant motor subtypes (tremor or non-tremor subtypes),[11] presence of depression[2] and clinical characteristics (eg, age, duration of PD and age at onset).[11–13] Patients with PD with non-tremor motor subtypes (66–74% of patients with PD) or depression (about 40% of patients with PD) generally show more or more severe cognitive impairments than patients with PD with tremor subtypes or patients with PD without depression.[14–16] Moreover, advanced age has been linked to more severe cognitive deficits (particularly in memory, language and visual functions) in PD.[17] Although age and duration of PD are correlated, the effect of disease duration on cognitive abilities in PD is more controversial. A few studies have shown that PD duration is unrelated to cognitive decline,[18 19] while others found that patients with a longer duration of PD are more likely to be demented.[20 21] Furthermore, some studies have shown that patients with early onset PD functioned cognitively better than those with late onset PD, despite equivalent age,[11 22] while others found younger age of PD onset to be related to increased cognitive deficits.[23]

To date, there is no consensus about the factors that are associated with cognitive heterogeneity in PD and it is still unclear why some patients with PD but without dementia have cognitive deficits and others do not. Some factors, such as the nature of dominant motor symptoms and the presence of depression, seem more likely to be associated with cognitive differences observed among individuals with PD, as suggested in many studies.[15 24 25] Therefore, this paper focuses on cognitive heterogeneity (ie, on the presence and the severity of global cognitive impairments) in PD without dementia according to: (1) predominant motor subtypes and, (2) the presence of depression.

Goals of the study

A meta-analysis was conducted to quantify the strength of the association between depression, predominant motor subtype and cognitive impairments

observed in participants with idiopathic PD without dementia. Only comparative research design studies were selected. Effect sizes (a measure of the strength of the relationship between two variables) were calculated for each factor and then compared to determine if the association between motor symptoms and cognitive abilities (such as language, visuospatial function and memory) is stronger than the relationship between depression and these cognitive capacities. This meta-analysis is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[26]

METHODS

A meta-analysis was performed to calculate effect sizes on cognitive capacities between PD subgroups with tremor-dominant (TD) and non-TD (NTD) motor subtypes, and between depressed (D-PD) and non-depressed (ND-PD) subgroups with PD. As authors of most studies published between 1989 and 2012 have used the Mini-Mental State Examination (MMSE) to evaluate cognitive capacities of subgroups with PD, MMSE score was chosen as the standard measure of cognition. The MMSE is a short 30-point questionnaire used to evaluate the level of cognitive functioning in different domains and has been demonstrated to be a valid cognitive screening tool for detecting global cognitive deficits in PD.[27 28] It has been recommended by the Movement Disorder Society Task Force for detecting 'impairment of more than one cognitive domain'.[28 29] This test is divided into two sections: the first section (maximum score=21) is devoted to the screening of orientation to time and space, memory, calculation and attention; the second section (maximum score=9) covers language abilities (naming, following verbal and written commands, and writing a sentence spontaneously) and visuoconstructional abilities (copying a complex polygon). Lower scores on the MMSE indicate poorer performance and greater cognitive deficits. Available in 58 languages, short and easy to administer, the MMSE is a widely used screening measure for detecting cognitive impairments in PD.[28]

Literature search

We identified potentially eligible studies about predominant motor subtypes and depression in PD through the US National Library of Medicine electronic database (PubMed) covering the period from 1989 to November 2012. The following keywords were first used in PubMed Advanced Search Builder to find eligible studies with TD and NTD motor subgroups: (motor subtype OR rigidity OR tremor) AND Parkinson's disease AND (MMSE OR cognition). New keywords were then used to retrieve studies about depression in PD: (depressive symptoms OR depression) AND Parkinson's disease AND (MMSE OR cognition).

Study selection

All potentially relevant studies found in PubMed were reviewed if they met the inclusion criteria presented below. A first screening of titles and abstracts was done to determine whether studies possibly matched the selection criteria. If the study passed the initial screening, the whole text of the article was retrieved. Then, to ensure finding all relevant studies, citations related to each eligible study were examined and all references in the articles retrieved were evaluated. Another search was done in Proquest Dissertation and Theses (with the terms previously used in PubMed) to found unpublished studies.

Inclusion criteria

A study was included in the meta-analysis if it met the following six criteria:

1. Patient subgroups consisted of adults diagnosed with idiopathic PD;
2. There were at least two PD subgroups in the study: (i) with different motor subtypes (TD and NTD motor subtypes) or (ii) with and without depression;
3. Outcomes included MMSE scores convertible to effect size (ie, means (M) and SD or exact statistical test results, F values, t values, z values or p values) and number of participants in both subgroups;
4. PD subgroups with TD and NTD motor subtypes were based on results obtained with the Unified Parkinson's Disease Rating Scale (UPDRS-III)[30] or obtained from subject report during clinical interview, confirmed through retrospective medical chart review.
5. PD participants were divided into two subgroups with or without depression according to the third or fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III or DSM-IV) criteria for minor or major depression.[31] Studies could also use other recognised tests such as the Hamilton Rating Scale for Depression (HDS),[32] Montgomery-Asberg Depression Rating Scale (MADRS),[33] Geriatric Depression Scale[34] or Beck Depression Inventory (BDI[35] and BDI-II[36]) to screen for depression.
6. Paper was published in English or French.

Studies that did not meet the inclusion criteria were excluded.

Data collection process

Relevant data in each eligible study was collected and recorded on an Excel spreadsheet. There was no missing information to calculate effect sizes in the eligible studies, so it was not necessary to contact authors. The principal outcome of the studies was the MMSE score (difference in means between PD subgroups: TD and NTD motor subgroups or depressive and non-depressive subgroups). MMSE score for each subgroup was recorded to compute the effect size associated with each study retrieved. Additional data was also collected such as the number of participants in each subgroup and the mean age, duration of PD and age at onset of the subgroups (three characteristics particularly known to influence cognitive functions in PD).

Statistical analysis

The meta-analysis was conducted in three steps.

1. An overall mean effect size was computed for all the studies, (i) with TD and NTD motor subgroups, and (ii) subgroups with and without depression on cognitive performances (MMSE scores). To ensure independence in the dataset, each study could be counted only once in the computation of the mean effect size.[37] Correlation coefficients were transformed using the Fisher transformation and all operations were performed on the Fisher's Zr. Unweighted and weighted (for the number of participants in each study) effect sizes (Pearson's r and Cohen's d) were subsequently calculated. The r value characterises the degree of correlation between two variables (ie, TD and NTD motor subtypes or the presence and absence of depression in PD), and the variable of interest (ie, performance on the cognitive measure) while the d value exemplifies this relationship in terms of the standardised difference between these two variables (calibrated according to the SD). The indices of central tendency chosen were the weighted mean d to facilitate comparisons

with other published meta-analysis.[38] Cohen's d shares the same range as SD (−3.0 to 3.0). To interpret the importance of a particular effect in concrete terms, Cohen's guidelines were adopted.[39] These suggest that a d value between 0.2 and 0.3 might be interpreted as a small effect, around 0.5 as a medium effect and 0.8 or more as a large effect.

2. Two χ^2 tests were also performed to examine homogeneity of the effect sizes included in this meta-analysis (for predominant motor subtypes and for depression). This procedure, as described by Rosenthal,[37] is equivalent to the calculation of Q_B as performed in other meta-analytic strategies. A significant result is an indication of the presence of moderator variables within the dataset.
3. Subsequently, a statistical comparison was made between the overall weighted effect size associated with predominant motor subtypes and the one associated with depression. CIs, established at 95%, were obtained for a fixed-model effect. All data collection, computations and analysis were done using Excel.
4. Finally, when the data distribution was not homogenous, we investigated to determine if different variables (age, duration of PD and age at onset) known to influence cognitive abilities in PD[12 13] might play a moderator role on the difference between the MMSE score of each subgroup. Relationships between these demographic variables and the effect sizes were investigated with the Spearman rank correlation test because the effect sizes were not normally distributed. All correlation analyses were performed with SPSS (Statistical Package for Social Sciences).

Risk of bias

Risk of bias in each study was evaluated using a methodological evaluation scale. The scale initially elaborated by Poynard (1988) and modified by Audet *et al*[40] was selected among several published scales to evaluate the quality of the studies included in the meta-analysis because it is short, has a good inter-rater reliability and presents a good content validity.[41 42] The final version of the scale used in this study was modified directly from Audet *et al*'s scale, which is composed of 17 items. Three items were removed, either because they were not applicable or because no study in this meta-analysis reported this information (see online supplementary figure A in web only files, which presents the methodological evaluation scale). A score in per cent was attributed to each study (see online supplementary figure A in web only files for the scoring method). A study with a score of 60% or more was judged acceptable.[40]

To evaluate risk of bias across studies, funnel plots of the effect sizes according to their simple size were used.[43] Degree of funnel plots asymmetry was measured with Egger's regression test.[44] This test indicates asymmetry if the intercept is significantly different from zero.

RESULTS

Study selection

The search in PubMed provided 168 references for predominant motor subtypes and 460 references for depression. Following the above methodology, 47 titles for predominant motor subtypes and 86 for depression were then selected and found in full text. Finally, 118 studies (42 for motor subtypes+76 for depression) were excluded because they did not meet the inclusion criteria. Reasons for exclusion are indicated in figures 1 and 2. For dominant motor symptoms, five studies from PubMed and eight studies identified through references and related citations were finally included in the meta-analysis. Ten studies about depression in PD found in PubMed were eligible and four studies fulfilling the selection criteria were identified through references.

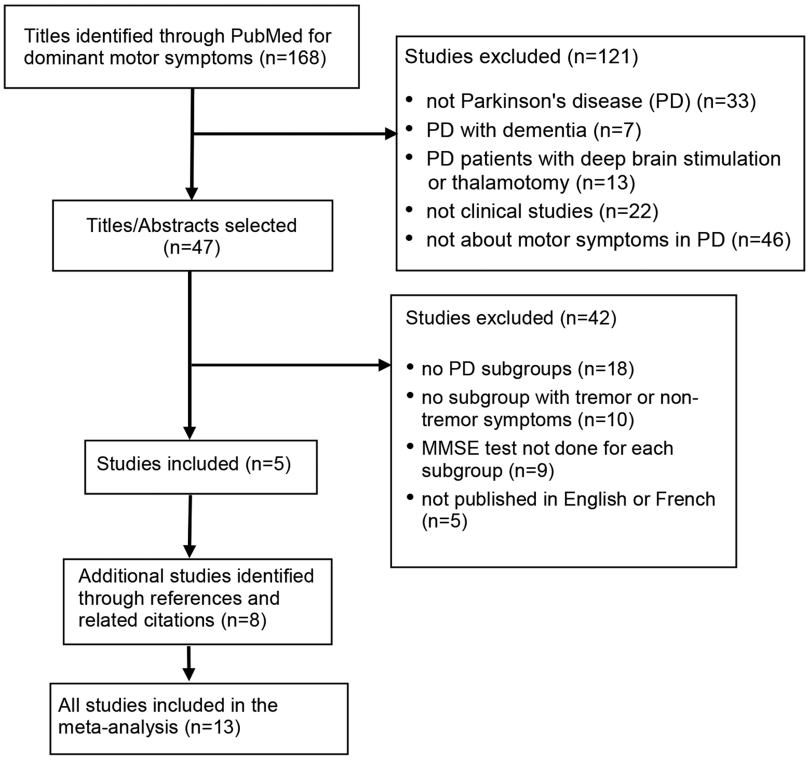

Figure 1 Literature search flow and main exclusion criteria for studies about dominant motor symptoms.

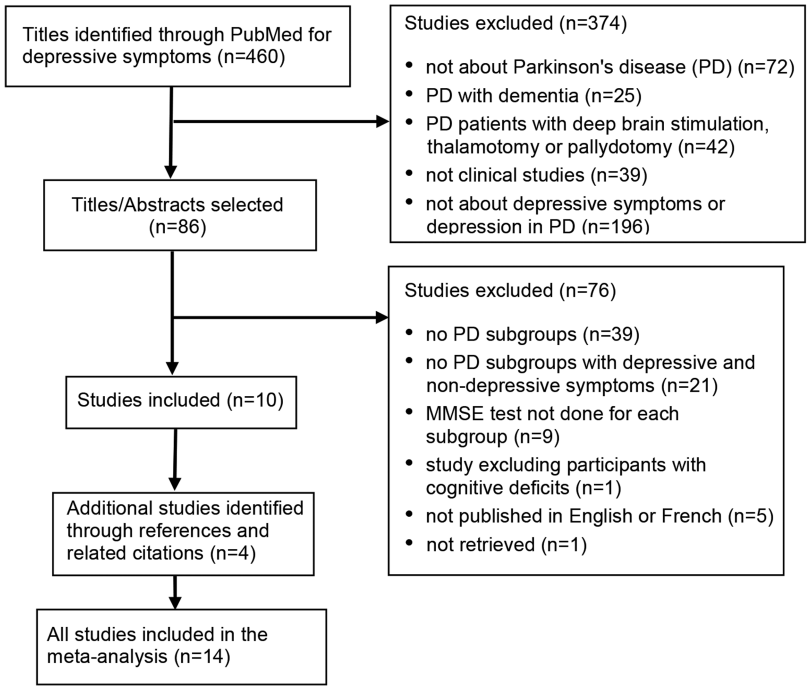

Figure 2 Literature search flow and main exclusion criteria for studies about depression in PD.

Studies and participants' characteristics

A total of 27 studies were included in the meta-analysis: 13 studies with TD and NTD motor subgroups published between 1991 and 2011 and 14 studies with D-PD and ND-PD subgroups published between 1989 and 2011 (see online supplementary Appendix 1 in web only files for references of the studies included in this meta-analysis). Selected studies about predominant motor symptoms separated participants with PD into subgroups according to their UPDRS-III score (10 studies), or according to subject report during clinical interview (1 study). Two studies formed their subgroups with a cluster analysis and then described their subgroups as tremor or non-tremor motor subtypes according to their UPDRS-III score. In studies about depression in PD, participants were diagnosed with depression according to the DSM-III or DSM-IV criteria (8/14), the HDS score (4/14), or the DSM-III criteria and the MADRS score (1/14). Geriatric Depression Scale score was also used in one study to separate PD participants with major depressive symptoms from those without depressive symptoms, but the diagnosis of depression was not confirmed by other tests.[45] BDI was sometimes used in addition to the DSM criteria to evaluate depressive symptoms' severity.

In total, data from 574 and 537 participants with TD and NTD motor symptoms, and 318 and 628 participants with and without depression, respectively, were used in the analyses (see online supplementary table A in web only files, which presents clinical characteristics of each subgroup with PD in each study reported in this meta-analysis). In the studies with TD and NTD motor subtypes, t tests for independent samples showed that participants did not differ significantly with regard to their age (TD: M=65.9, SD=5.9 vs NTD: M=65.7, SD=7.9; df=24; p=0.91), the duration of PD (TD: M=7.4 years, SD=2.7 vs NTD: M=7.0, SD=2.0; df=22; p=0.67) or their age at onset (TD: M=59.0, SD=4.3 vs NTD: M=59.3, SD=2.6; df=22; p=0.87). In the studies with D-PD and ND-PD subgroups, the mean age (D-PD: M=66.8, SD=2.8 vs ND-PD: M=66.7, SD=3.1; df=26; t=0.06; p=0.95), the duration of PD (D-PD: M=8.8 years, SD=3.0 vs ND-PD: M=7.3, SD=1.7; df=18.9; t=1.63; p=0.12) and the mean age at onset (D-PD: M=57.8, SD=4.8 vs ND-PD: M=59.3, SD=4.1, df=24; t=–0.89; p=0.39) were also comparable in both subgroups.

Risk of bias in individual studies

According to the methodological evaluation scale adapted from Audet *et al*,[40] all studies included in this meta-analysis had an acceptable quality score (61.5% or more). The mean score (±SD) for the methodological quality of analysed studies with TD and NTD subgroups was 66.6±5.1% (range 61.5–76.9) while studies about depression had a mean score of 69.0% ±7.6% (range 61.5–84.6). In total, 19 studies had a score between 60% and 70%, while 8 studies had a score higher than 70%. In many studies, the authors did not mention if the participants or the persons administering the evaluations were blind to the aim of the study. However, since this meta-analysis was not about the effect of a treatment and since evaluating global cognitive functions (with the MMSE) was not the main goal of the analysed studies, these criteria should not have an important impact on the quality of the results. Moreover, 17 papers did not report the number of excluded participants, but the other criteria were met in the majority of the studies.

Risk of bias across studies

The funnel plot for studies about dominant motor symptoms (see online supplementary figure B in web only files) was symmetrical according to the Egger's regression test. Indeed, the intercept did not differ significantly from zero (2.10 (95% CI –1.74 to 5.94), p=0.25). A similar result was obtained for studies about depression (see online supplementary figure C in web only files). Egger's regression test also showed that the funnel plot was symmetrical (intercept: 1.24 (–2.45 to 4.92), p=0.48). The symmetry in both funnel plots seemed to indicate an absence of publication bias. However, the effect sizes heterogeneity and the small number of studies in this meta-analysis required us to be cautious about the interpretation of these results.

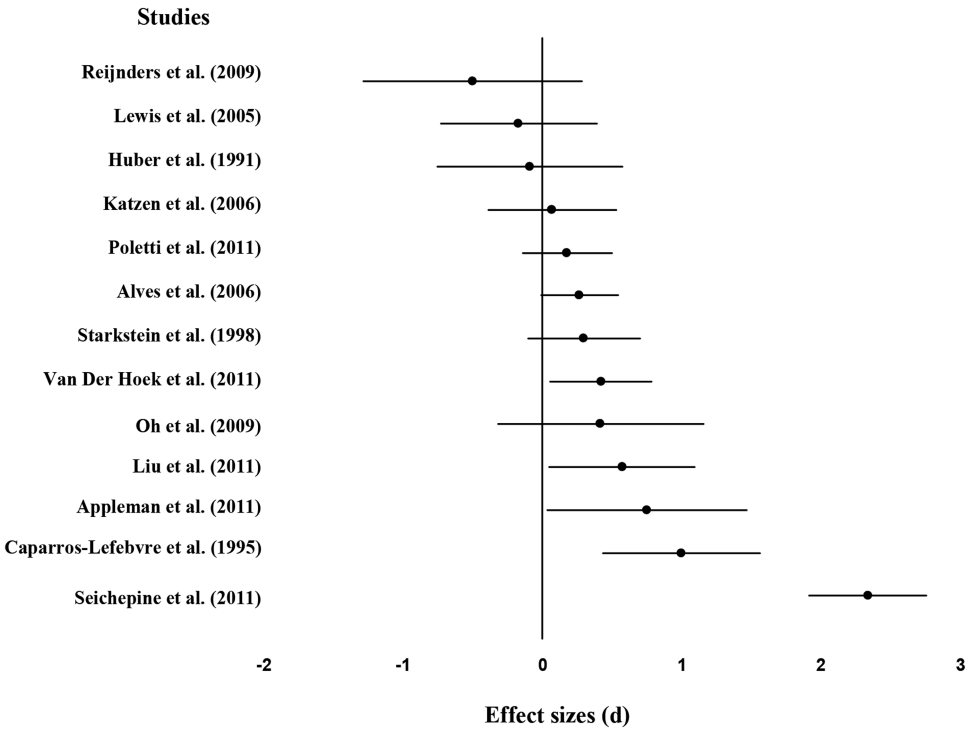

Figure 3 Forest plot of the mean effect sizes (Cohen's d) for each study with subgroups divided according to their predominant motor subtype. Horizontal lines are 95% CIs for individual studies.

Overall effect sizes for predominant motor subtypes and depression

Figure 3 presents the effect sizes (Cohen's d) associated with predominant motor symptoms calculated from each study while figure 4 shows the effect sizes associated with depression. An effect size (d value) of zero indicates no cognitive difference between PD subgroups while an effect size of 3 or −3 indicates that PD subgroups are completely different cognitively. Positive effect sizes indicate that PD subgroups with NTD motor subtype or with depression had more cognitive deficits than PD subgroups with TD motor subtype or without depression while negative effect sizes indicate the opposite. d Values range from −0.52 to 2.09 in studies with NTD and TD subgroups and from −0.42 to 2.27 in studies with ND-PD and D-PD subgroups. The unweighted average effect sizes (Cohen's d and Pearson's r) were first calculated for predominant motor subtypes (d=0.38

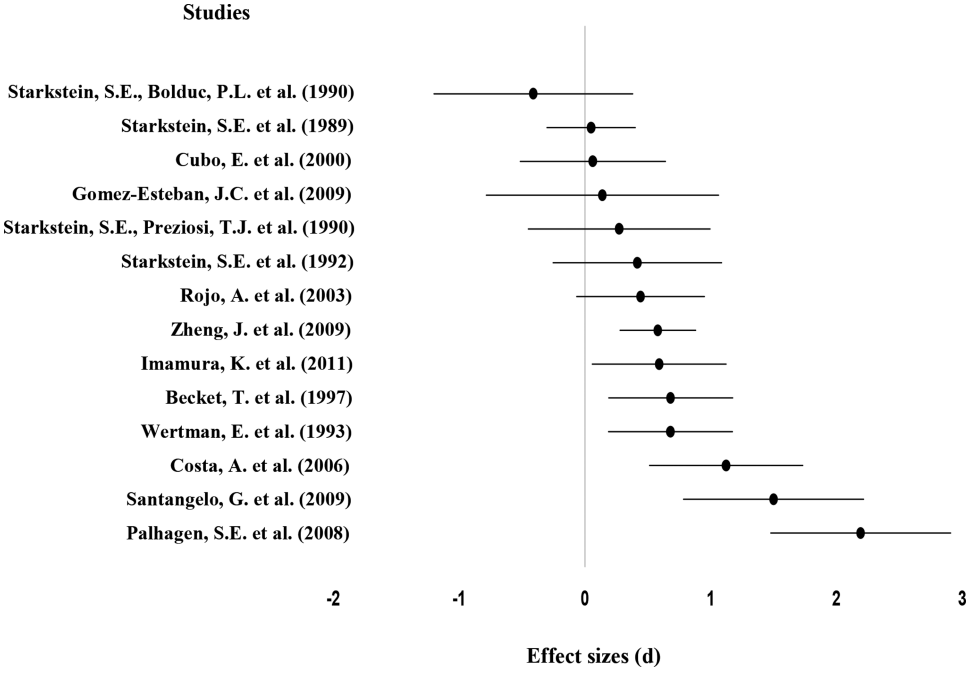

Figure 4 Forest plot of the mean effect sizes (Cohen's d) for each study with subgroups divided according to the presence or absence of depression. Horizontal lines are 95% CIs for individual studies.

(95% CI 0.03 to 0.73); r=0.19 (95% CI 0.05 to 0.33)) and depression (d=0.59 (95% CI 0.24 to 0.94); r=0.27 (95% CI 0.15 to 0.39)) (see online supplementary table B in web only files, which presents effect sizes associated with each study included in this meta-analysis). Subsequently, the weighted average effect sizes for the number of participants in each study were also computed for these two factors. Table 1 presents the weighted mean effect sizes (Cohen's d and Pearson's r) of predominant motor subtypes (d=0.42 (95% CI 0.30 to 0.54); r=0.21 (95% CI 0.15 to 0.27)) and depression (d=0.52 (95% CI 0.38 to 0.66); r=0.25 (95% CI 0.19 to 0.31)) on MMSE results. All the mean effect sizes were significantly different from zero ($p<0.05$). Predominant motor subtypes had a small to medium average effect size while depression had a fairly medium effect size according to Cohen's guidelines (see Methods). No significant difference between weighted mean effect sizes for predominant motor subtypes and depression ($\chi^2_1=1.22$; $p=0.27$) was observed although the mean effect size for depression was higher. The probability associated with the homogeneity statistic was significant for the predominant motor subtypes' effect sizes ($\chi^2_{12}=66.4$; $p<0.001$) and the depression's effect sizes ($\chi^2_{13}=30.9$; $p=0.004$), indicating a heterogeneity in the studies' results that could be caused by the presence of moderator variables.

Effects of clinical variables

Associations between three clinical characteristics known to influence cognitive abilities in PD (age, duration of PD and age at onset) and the effect sizes were investigated with the Spearman rank correlation test. For each of these characteristics, the mean of the two subgroups in each study was calculated (eg, (mean age of subgroup 1+mean age of subgroup 2)/2) to verify if younger or older subgroups, more or less long duration of PD, and younger or older age at onset, might affect the effect sizes associated with predominant motor subtypes or with depression. Overall mean and SD of the subgroups (separated according to dominant motor symptoms or the presence of depression) were calculated for age (65.8±4.8 and 66.8±2.9 years, respectively), duration of PD (7.2±2.2 and 8.1±2.5 years, respectively) and age at onset (59.1±3.4 and 58.5±4.4 years, respectively). Spearman's correlation coefficients between these three variables and the effect sizes were calculated, but no significant correlation was found. Thus, effect size heterogeneity between studies about predominant motor subtypes and depression in PD seems to be caused by factors other than age, duration of PD or age at onset.

DISCUSSION

The aim of this meta-analysis was to compare the MMSE score obtained by different subgroups (NTD vs TD, D-PD vs ND-PD) of PD to identify possible differences in overall cognition. This meta-analysis showed that patients with PD with NTD symptoms or depression were more cognitively impaired than patient with TD symptoms or without depression, respectively, as indicated by the effect sizes calculated (d=0.42 for predominant motor symptoms and d=0.52 for depression). Even if these mild to moderate effect sizes seem different, they are statistically comparable. This means that the cognitive difference between NTD and TD subgroups is comparable with that between D-PD and ND-PD subgroups. One might think that NTD and D-PD subgroups are, in fact, the same subgroup because NTD symptoms and depression seem to have a similar association with cognitive impairments and NTD subgroups are more likely to be depressed. However, the nature and severity of cognitive deficits in addition to the neuropathological lesions differentiate the NTD and D-PD subgroups. The concept of different clinical phenotypes in PD has been discussed in the literature with regard to distinct neuropathological lesions and specific neuronal systems degeneration, but there is no consensus about what might explain cognitive heterogeneity in PD.[46]

Predominant motor symptoms

This meta-analysis confirms that patients with PD with NTD symptoms generally have lower MMSE scores than patients with TD symptoms. Previous studies indicated that NTD subgroups had specific cognitive dysfunctions that were not present in TD subgroups.[4] For example, Huber *et al*[47] demonstrated that only patients with rigid/bradykinetic PD had visuospatial and phonemic verbal fluency impairments while Lewis *et al*[48] observed that the NTD subgroup was the only one to demonstrate planning and spatial recognition memory difficulties. Cognitive differences between motor subgroups suggest the presence of different neuropathological lesions among individuals with PD. Indeed, the NTD subtype seems to be associated with more widespread cognitive impairment and neuronal degeneration than the TD subtype.[46] Patients with NTD symptoms are likely to have more severe neuronal loss in the ventrolateral part of the substantia nigra zona compacta and more profound dopaminergic depletion in the posterior putamen.[16] This would result in inhibition of the thalamus and decreased activation of the cortex. Reduced cortical activity would ultimately lead to impaired cognitive abilities.

Although many studies have shown cognitive and anatomical differences between patients with TD and NTD symptoms, heterogeneous effect sizes were observed in this meta-analysis. This heterogeneity indicates that the difference between the MMSE results of TD and NTD subgroups varies among studies. However, no study demonstrated that patients with TD symptoms had more cognitive deficits. Some studies observed more cognitive impairments in patients with NTD symptoms (6/13) while others did not find significant cognitive differences between subgroups (7/13). Examination of the impact of different demographic variables indicates that age, duration of PD

Table 1 Weighted mean effect sizes associated with non-tremor dominant (NTD) and TD motor subtypes, and Parkinson's disease subgroups with (D-PD) and without (ND-PD) depression on cognitive abilities

	Number of participants in each subgroup		Number of studies	Mean effect sizes (SD)		Medians		IQRs (Q3–Q1)	
Criteria for subgroups comparison	NTD/D-PD	TD/ND-PD	K	d*	r	d	r	d	r
Predominant motor subtypes	574	537	13	0.42 (0.21)	0.21 (0.11)	0.30	0.15	0.50	0.24
Depression	318	628	14	0.52 (0.27)	0.25 (0.11)	0.51	0.25	0.51	0.24

*Cohen's guideline: d≈0.2–0.3 (small effect); d≈0.5 (medium effect); d≥0.8 (large effect).

and age at onset did not explain the heterogeneous results between studies.

Nevertheless, other variables like depression could have affected the effect sizes measured in each study. Interestingly, 6/13 studies did not find any difference between the depression severity scores of the TD and NTD subgroups; 6/13 studies reported that the NTD subgroups showed significantly more severe depressive symptoms than the TD subgroups while only 1 study in 13 excluded depressive patients. Half of the studies reporting a difference in depressive symptoms between NTD and TD subgroups (3/6) also found a difference in cognitive capacities between these same subgroups. Moreover, among these studies, two found that the cognitive differences observed between TD and NTD subgroups remained significant using depression scores as a covariate.

Depression

The results of this study also suggested that PD subgroups with depression had more severe cognitive impairments than patients with PD without depression. No study showed that ND-PD subgroups had more severe cognitive deficits than subgroups with depression. However, half of the analysed studies reported that D-PD subgroups had a significantly lower MMSE score than ND-PD subgroups. Depression in PD seems to aggravate specific cognitive impairments already present in PD, such as executive, language and memory deficits.[15 49] Indeed, Wertman *et al*[50] observed that patients with D-PD performed worse than ND-PD individuals on set shifting and selected memory tasks. However, it is difficult to determine if cognitive differences between patients with D-PD and patients with ND-PD are a manifestation of depression or if these differences are associated with a specific profile in PD. Kuzis *et al*[51] compared patients with D-PD and individuals with major depression (MD) but without PD and reported that patients with D-PD had a worse performance than individuals with MD on different cognitive tasks such as concept formation and switching abilities. Their results suggested that cognitive deficits in the D-PD group were associated with depression, and may be related to more extensive neuropathological impairments in patients with PD with depression. Indeed, Paulus and Jellinger[52] showed that the density of neurons in the dorsal raphe nucleus is lower in patients with D-PD than in patients with ND-PD. According to Lieberman,[53] the decrease in the number of serotonergic neurons in the dorsal raphe nucleus may be partly responsible for the presence of depressive symptoms in PD. This suggests that depression might not be simply a reaction to having PD, but might be caused by the neuronal degeneration in PD.

Similarly to predominant motor subtypes, effect sizes related to depression in PD were heterogeneous, indicating that the differences between the MMSE scores of D-PD and ND-PD subgroups vary between studies. None of the three characteristics analysed in this study (age, duration of PD and age at onset) had an impact on the cognitive heterogeneity observed. Nevertheless, this heterogeneity may be explained by other factors such as depressive symptoms severity, the test used to evaluate depression and the stage of the disease. Depression severity could have an impact on the cognitive abilities measured because participants with PD with less severe depressive symptoms have generally less pronounced cognitive impairments than patients with PD with severe depression.[50]

In this meta-analysis, three studies included participants with minor depression in the subgroup of PD with depression. However, most of the studies (11/14) compared a ND-PD subgroup with PD participants with MD. The criteria for MD differed between studies and were dependent on the test used to evaluate depression. The fact that studies used different tests (eg, HDS, MADRS, BDI, etc) and cut-offs to evaluate depression severity may partly explain the different results observed because the subgroups were not defined in the same way in all the studies. In addition, the stage of the disease in each PD subgroup may have influenced the effect sizes measured. Although most studies had comparable subgroups according to the stage of the disease, the mean stage of each subgroup varied from one study to another.

As this meta-analysis suggests that patients with NTD motor subtype might have more cognitive deficits than patients with TD subtype, the predominant motor subtype of each D-PD and ND-PD subgroup was investigated. However, only 2/14 studies with D-PD and ND-PD subgroups mentioned the number of patients with TD and NTD. In these two studies, there was no significant difference between the percentage of patients with TD and NTD symptoms in the D-PD and ND-PD subgroups.

Meta-analysis limitations

One limitation of this meta-analysis is that depression severity, stage of the disease and severity of the motor symptoms were not taken into account in the effect size calculations. These variables might partly explain the heterogeneity reported in the results. However, the studies analysed in this meta-analysis did not present enough consistent data to verify quantitatively the impact of these variables on the effect sizes measured. It is difficult to compare depression severity scores between studies because depression severity was not evaluated by the same test or the same cut-off score. Moreover, the stage and severity of the disease were not taken into account because the articles analysed in this meta-analysis did not consistently report these factors for each subgroup. The mean stage of the disease, according to the Hoehn and Yahr[54] scale, for D-PD and ND-PD subgroups was not reported in 4 out of 14 studies, while it was not mentioned explicitly in 4 out of 13 studies with TD and NTD subgroups. Some studies reported the mean of total motor scores (UPDRS-III) for each subgroup, other studies only mentioned the score for tremor, rigidity and akinesia separately, and six studies did not report (quantitatively) any motor symptom severity. Moreover, this meta-analysis did not take into account studies in which tests other than the MMSE (eg, Montreal Cognitive Assessment test or PD-Cognitive Rating Scale) were used to evaluate overall cognitive capacities of subgroups with PD.[55 56] This was done on purpose to compare studies more easily and to diminish the variability associated with results obtained in different cognitive tests. Another limitation of this study lies in the fact that the MMSE is a test for assessing global cognitive abilities. Therefore, using this test does not warrant the identification of mild impairment affecting one or more specific cognitive abilities. Thus, it would be interesting to investigate more deeply the specific cognitive impairments of patients with D-PD and NTD with extensive neuropsychological test batteries.

CONCLUSION

To the authors' knowledge, this is the first study performed to quantify and compare the strength of association between dominant motor subtypes, depression and cognitive deficits observed in PD. This meta-analysis reported a significant, but slight to moderate association between dominant motor subtypes and cognitive impairments, and a moderate association between depression and cognitive dysfunctions in PD. This study suggests that D-PD individuals are cognitively different from ND-PD individuals, just as patients with NTD symptoms seem to differ from patients with TD symptoms. Recent researches about MCI in PD have led

us to believe that some patients with PD with NTD or depression and cognitive impairments might actually be considered as MCI, but none of the studies analysed in this meta-analysis reported this information.[7 8] It seems that individuals with PD cannot be considered to be a homogenous group and it might be important to take into account the presence of depression and the subtype of predominant motor symptoms when evaluating cognitive abilities in PD. The variability in cognitive impairments in PD suggests the existence of distinct subgroups with different clinical patterns and neuropathological mechanisms. Better knowing the impact of different features of PD may improve our understanding of different syndromes of PD, and could help to better counsel and manage patients with PD. Indeed, this could help clinicians choosing the best treatment for individuals with PD (eg, pharmacotherapy, electrical stimulations, etc).

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The heterogeneity of cognitive symptoms in Parkinson's disease: a meta-analysis

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