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Review article

Cognitive and neuroanatomical correlates of neuropsychiatric symptoms in Parkinson's disease: A systematic review

Hamad Alzahrani [a,b], Annalena Venneri [a,c,*]

[a] Department of Neuroscience, Faculty of Medicine, University of Sheffield, UK
[b] National Neuroscience Institute, King Fahad Medical City, Riyadh, Saudi Arabia
[c] IRCCS Fondazione Ospedale San Camillo, Venice, Italy

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ABSTRACT

Introduction: Neuropsychiatric symptoms are one of the most common non-motor symptoms in Parkinson's disease (PD). These symptoms have a negative impact on daily living activities and cognitive abilities. This review will be centred on published articles which focused on clarifying the cognitive and neuroanatomical features associated with the appearance of specific neuropsychiatric symptoms in this disease.
Methods: All articles indexed in the Web of Science and PubMed databases were reviewed for potential inclusion in October 2014. In the first stage of the review, we identified 41 articles that investigated neuropsychiatric symptoms and cognitive impairments in PD. In the second stage, there were 26 published articles on the neural bases of neuropsychiatric symptoms in PD.
Results: The main findings revealed that executive dysfunctions were common in patients with depression, apathy, visual hallucinations (VH), impulse control disorders (ICDs) and anxiety, whereas, memory deficits were associated mainly with depression and VH. Imaging studies have shown that frontal lobe atrophy was frequently observed in patients with depression, apathy, VH and ICDs.
Conclusion: This review gives a snapshot of those cognitive and neural correlates of neuropsychiatric symptoms in PD. Methodological shortcoming in the available studies were identified, however, of which the most critical appeared neglecting the presence of multiple neuropsychiatric symptoms in some of the patients included in studies of specific individual symptoms. Additionally, in most studies only patients in the moderate to severe stages were included which limits possible inferences to the early stage of the disease.

Contents

* Corresponding author at: Department of Neuroscience, Medical School, University of Sheffield, Beech Hill Road, Sheffield S10 2RX, UK.
E-mail address: a.venneri@sheffield.ac.uk (A. Venneri).

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1. Introduction

Neuropsychiatric symptoms are common in patients with Parkinson's disease (PD). A recent published study reported that 89% of PD patients with dementia presented with at least one neuropsychiatric symptom [1]. These symptoms cause impairments in daily living activities equal to or more than the limitations that result from motor deficits, and may lead patients to earlier admission to residential care [2–4]. Neuropsychiatric symptoms also occur even in the early stages of the disease. Prior research has suggested that these symptoms frequently go unrecognised by clinicians and remain untreated [5].

It has been reported that neuropsychiatric symptoms have a negative impact on cognitive abilities in PD patients. However, the link between the presence of specific neuropsychiatric symptoms and specific cognitive impairments needs to be reviewed to gain a thorough understanding of the neural bases of specific symptoms, since prior studies used different methodologies and consequently produced inconsistent findings. Existing review articles on this topic focused mainly on a few neuropsychiatric symptoms and reviewed only either the neuropsychological or the neural correlates of those symptoms in PD, but did not cover the range of possible symptoms that can be observed in this disease and did not look for a parallel between brain atrophy or dysfunction and cognitive deficits within the same sample of patients [6–12].

The present review will cover the most common psychiatric manifestations observable in PD, and will also attempt a comprehensive overview of their cognitive and neural aspects. More specifically, the review will cover depression, apathy, psychosis, impulse control disorders (ICDs) and anxiety [13]. In detail the review addresses some important issues including how specific neuropsychiatric symptoms may affect cognitive abilities in patients with PD; and what specific regional brain atrophy or dysfunction may underlie a specific symptom in this disease. The review will highlight any limitations in the literature which might be helpful to suggest directions for future work.

2. Method

Articles were identified by carrying out a comprehensive review of published research papers that have investigated the cognitive and neural correlates of neuropsychiatric symptoms in PD. The present online literature search of the Web of Science and PubMed databases was carried out in October 2014. This search was completed in two stages; the time span for the first stage of search was from 1986 to 2014, whereas for the second stage was from 1994 to 2014. Firstly, a search for published papers about neuropsychiatric symptoms and cognitive impairments in PD was carried out using the following keywords: Parkinson's disease, neuropsychiatric symptoms, depression, apathy, psychosis, hallucinations, impulse control disorders, anxiety, cognitive impairments and cognitive decline. The initial search identified 1275 titles and abstracts. Then we excluded 217 duplicate publications. The abstracts and full reports were reviewed to eliminate articles according to the following exclusion criteria: (1) studies that did not focus on cognitive abilities, for instance some studies were focused on other aspects such as prevalence, clinical correlates and managements, (2) review articles, (3) papers that did not include patients with a diagnosis of PD, (4) the investigation of other non-motor symptoms or other neuropsychiatric symptoms that were not specified in this review, (5) non-peer reviewed articles and (6) articles which were not written in the English language. In total, 41 articles met our inclusion criteria (see Fig. 1 and Tables 1, 2 and 3).

The second stage was to look for published articles on the neural bases of neuropsychiatric symptoms in PD using the same key words except for the words cognitive impairments and cognitive decline but including magnetic resonance imaging (MRI), voxel-based morphometry (VBM), single photon emission computed tomography (SPECT) and positron emission tomography (PET) instead. We identified 338 titles and abstracts, and then we excluded 43 duplicate articles. Almost the same exclusion criteria for the first stage were used for the second stage of the review. Specifically, criteria 2 to 6 were used, but also articles that did not use any neuroimaging techniques had to be excluded. After applying these exclusion criteria there were 26 studies that met criteria (see Fig. 2 and Table 4).

3. Results

According to Aarsland et al. [14] the overall prevalence of neuropsychiatric symptoms in PD patients is 61%. The most common symptoms are depression (38%), hallucinations (27%), anxiety (20%) and apathy (16.5%). The less common symptoms are euphoria (7.0%) and disinhibition (6.5%). A more recent study [15] found that the prevalence of neuropsychiatric symptoms in early untreated PD patients was 56%. The most common symptoms reported in this study were depression (37%), apathy (27%), sleep disturbance (18%) and anxiety (17%), whereas, psychotic symptoms were found to be very rare among untreated PD patients [15]. In PD patients with dementia the prevalence of neuropsychiatric symptoms was found to be higher. In the Aarsland et al. study, 50 out of 139 patients were demented [14] and in a further study, Leroi et al. [16] reported that 96% of PD patients with dementia presented with at least one neuropsychiatric symptom. Another study demonstrated an association between the total Neuropsychiatric Inventory (NPI) score [17] and depression and anxiety (as measured by the Hospital Anxiety and Depression Scale) [18] in non-demented PD patients. Also, the presence of neuropsychiatric symptoms was independently predicted by a longer disease duration and more severe stage of PD [19].

3.1. Cognitive correlates of neuropsychiatric symptoms in PD

3.1.1. Depression

Depression is the most common neuropsychiatric symptom in PD patients [15]. It has been indicated that the prevalence rate of depression in this disease is approximately 40% [14,20,21]. Several studies have demonstrated an association between depression and cognitive impairments in PD patients [22–30]. There are, however, a few other studies that did not detect a significant association between depression and variance in cognitive deficit in PD (See Table 1) [31–34]. In this disease, cognitive deficits may occur as a form of global cognitive decline or as an impairment of specific cognitive domains. For example, some researchers have found that higher depression scores negatively correlated with lower scores on the Mini Mental State Examination (MMSE) [23,24] (patients included in the first study [23] had mild to severe disease stages with an average disease duration of 7 years, whereas in the second study [24] patients had mild to moderate disease stages with an average disease duration of 8.45 years), the dementia rating scale [23,24,28] (in the third of these studies [28] patients had mild to severe disease stages with an average disease duration of 11.3 years, patients also were taking Levodopa medication), and the Wechsler Adult Intelligence Scale [29] (in this study patients had mild to moderate disease stages). However, these findings are not in line with other studies

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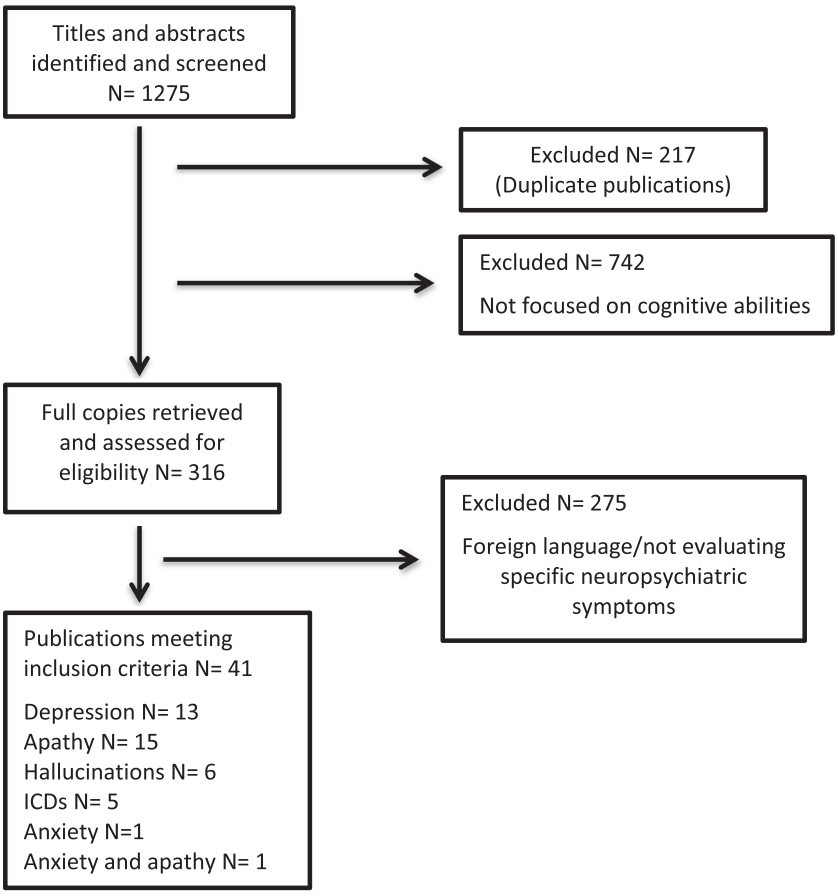

Fig. 1. Flow chart of study selection process (cognitive correlates of neuropsychiatric symptoms in PD).

that found no relationship between depression and overall cognitive skills in PD [22,27] (in both these latter studies patients had mild to moderate disease stages).

Deficits of specific cognitive domains in depressed PD patients mainly involved the impairment of executive functions, attention and memory. In terms of executive dysfunction, several studies have reported that patients with depression performed significantly lower than non-depressed patients on tests of executive function including the Wisconsin Card Sorting Test (WCST) [35], controlled word association test-FAS [36], Trail Making Test (TMT) (A and B) [37], verbal fluency, abstract reasoning, design fluency test (free condition) [38] and the symbol digit modalities [25,28,30,39]. Other studies have also demonstrated that depressed PD patients had lower scores relative to non-depressed PD patients using a variety of executive tasks e.g. letter fluency, abstract reasoning and card sorting test [22], category fluency test and TMT [29], set-shifting and response inhibition [40], Frontal Assessment Battery and Stroop test [27]. As for deficits in other cognitive domains, earlier studies have reported an association between depression and poorer scores on tasks of attention (assessed by a subtest of the dementia rating scale and digit span forward) [25,26], short-term memory (measured by digit span forward and backward) [30], and memory which was assessed by the word-list recall and recognition test [22], Hopkins verbal learning test [24,41], a subtest of the dementia rating scale [26] and the pattern recognition memory task [29]. In addition, another study indicated a relationship between depression and poorer performance on a range of cognitive tasks including those testing executive function (Trail Making Test), memory (Rey auditory verbal learning test) and visuospatial skills (Rey-Osterreith complex figure test) [42].

Despite the amount of research which has examined the association between depression and cognitive functions in PD, various shortcomings in these studies limit the validity of their conclusions. These limiting factors include failing to exclude patients who presented with multiple neuropsychiatric symptoms, a small number of participants in some studies and the use of screening instruments that measure limited cognitive functions. Furthermore, prior work did not focus on the early stages of the disease, most of the studies recruited patients with heterogeneous levels of severity ranging from mild to severe stages.

3.1.2. Apathy

In the literature, it has been demonstrated that apathy is associated with cognitive dysfunction [15,41,43–53] (See Table 2), depression [44–46,50,51,53–56] and anxiety [57]. Although apathy and depression can co-exist in PD, several studies have found that apathy may occur in isolation in the absence of depression [15,45,46,51,53,56,58–60].

Apathy in PD patients has been found to be associated mainly with executive dysfunction [15,41,44,45,49,52,53,57]. For instance, Aarsland et al. [14] examined cognitive functions in PD patients with and without dementia. Apathy was found to be significantly associated with dementia and with performance on an executive function task, i.e. the Stroop test [14]. Other studies found that apathy was significantly associated with executive dysfunctions, evaluated with the Executive Interview [61] and category and letter fluency [45] (in this study patients were treated with levodopa and their average disease duration was 4.3 years). Dujardin and colleagues [44] evaluated cognitive functions in non-demented PD patients (average disease duration was 9.4 years and they were treated with levodopa). They concluded that after an 18 month follow-up, apathetic PD patients had more cognitive deficits, mainly executive dysfunction (measured by the Stroop test) and were more likely to meet the criteria for dementia compared with non-apathetic PD patients [44]. Memory deficits have also been observed in apathetic PD patients without dementia. These were detected with

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Table 1
Summary of articles included in the review (cognitive performance in PD with depression).

Authors	NPSS	Number of participants	NPSS assessments	Cognitive domain targeted	Cognitive tests	Impaired cognitive performance
Taylor et al. [32]	Depression	15 PD with depression 15 PD without depression	Beck Depression Inventory (BDI) DSM-III	Short-term memory	Digit span	No differences
Starkstein et al. [28]	Depression	15 PD with major depression 19 PD with minor depression 44 PD without depression	Hamilton Rating Scale for Depression (HRSD) DSM-III	Global cognitive ability Executive function Attention	MMSE WCST TMT Digit span	All cognitive domains
Troster et al. [34]	Depression	45 PD with depressed 45 PD patients without depression	BDI	Conceptualisation initiation Construction memory	Subtests of Dementia Rating Scale	No differences
Troster et al. [33]	Depression	44 PD with depressed 44 PD patients without depression	BDI	Executive function Attention Memory Immediate and delayed recall	WCST Digit span Logical Memory Test part of WAIS Boston Naming Test	No differences
Kuzis et al. [25]	Depression	19 PD with depression 31 PD without depression 27 with depression only	HRSD	Executive function Attention Abstract reasoning	COWAT-FAS Digit span RPM	Verbal fluency Attention Abstract reasoning
Cubo et al. [23]	Depression	88 PD	HRSD	Global cognitive ability	MMSE	Global cognitive ability
Norman et al. [26]	Depression	35 PD	BDI	Global cognitive ability	DRS	Global cognitive ability
Uekermann et al. [30]	Depression	12 PD with depression 16 PD without depression 14 with depression only	BDI	Executive function Memory General intellectual functioning	Letter Fluency Test Digit span WAIS	Executive dysfunction Short-term memory Concept formation
Costa et al. [22]	Depression	18 PD with major depression 21 PD with minor depression 32 PD without depression	DSM-IV BDI	Global cognitive ability Memory Executive functions Abstract reasoning Visual–spatial Language	MMSE Word-list recall and recognition Letter Fluency Test RPM Coping Rey's figure form Sentence Construction Test	Global cognitive ability Long-term verbal episodic memory Abstract Reasoning Verbal fluency
Stefanova et al. [29]	Depression	16 PD with major depression 10 PD with minor depression 54 PD without depression	DSM-IV HRDS	Global cognitive functioning Memory Executive abilities Language Visual organisation	WAIS RAVLT TMT Letter and Category Fluency Tests Boston Naming Test Spatial Working Memory Test Pattern Recognition Memory Test	Global cognitive ability Verbal fluency Cognitive flexibility Working memory Language Spatial recognition
Silberman et al. [31]	Depression	18 PD with depression 28 PD without depression	DSM-IV HRSD	Executive function	Stroop test	Response inhibition Set-shifting
Santangelo et al. [27]	Depression	65 PD with depression 60 PD without depression	DSM-IV HRSD	Executive function	Stroop test FAB	Response inhibition Set-shifting Inhibitory control
Fernandez et al. [24]	Depression	82 PD	BDI	Global cognitive ability Attention Memory Processing speed Language Executive function Visual–spatial processing	MMSE DRS Digit span HVLT TMT Judgment of Line Orientation Test Face Recognition Test	Global cognitive ability Word-list delayed recall Language

NPSS: neuropsychiatric symptoms, DSM: Diagnostic and Statistical Manual of Mental Disorders, MMSE: Mini Mental State Examination, WCST: Wisconsin Card Sorting Test, TMT: Trail Making Test, WAIS: Wechsler Adult Intelligence Scale, COWAT: Controlled Oral Word Association Test, RPM: Revan's Progressive Matrices, DRS: Dementia Rating Scale, FAB: Frontal Assessment Battery, HVLT: Hopkins Verbal Learning Test.

tasks of immediate free recall, short and long delay free recall, long delayed cued recall, delayed recognition (evaluated by the California verbal learning test) [62], and digit span backward [52] (in this study patients had mild to severe disease stages, their average disease duration was 5.9 years and they were treated with levodopa). A recently published study showed that patients with akinetic-rigid type PD who manifested apathy performed significantly worse on tasks of frontal lobe function e.g. the FAB [63], letter fluency [64] and interference error on the Stroop test [65] compared with patients with tremor-dominant type PD [47].

A further study reported that in patients with PD with left-side onset (patients had mild to moderate disease stages, their average disease

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Table 2
Summary of articles included in the review (cognitive performance in PD with apathy).

Authors	NPSS	Number of participants	NPSS assessments	Cognitive domain targeted	Cognitive tests	Impaired cognitive performance
Starkstein et al. [51]	Apathy	45 PD	AES	Executive functions	COWAT-FAS	Verbal fluency
Levy et al. [46]	Apathy	40 PD 30 AD 28 Frontotemporal dementia 22 Progressive supra-nuclear palsy	NPI	Global cognitive ability	MMSE	Global cognitive ability
Aarsland et al. [14]	Apathy	139 PD	NPI	Global cognitive ability Executive functions	MMSE Stroop test	Global cognitive ability
Pluck & Brown [49]	Apathy	45 PD	AES	Executive functions	Stroop test COWAT-category test	Response inhibition Set-shifting Verbal fluency
Isella et al. [45]	Apathy	30 PD	AES	Executive functions	Letter and category fluency tests	Verbal fluency
Zgaljardic et al. [53]	Apathy	32 PD	AES	Executive functions	Letter and category fluency tests Digit span	Verbal fluency Attention
Dujardin et al. [44]	Apathy	20 PD with apathy 21 PD without apathy	LARS	Executive functions	Stroop test Letter and category fluency tests	Response inhibition Processing speed Verbal fluency
Reijnders et al. [50]	Apathy	55 PD	AES	Global cognitive ability	MMSE CAMCOG	No correlation
Butterfield et al. [41]	Apathy	68 PD	AES	Executive functions Memory	WCST HVLT-R	Problem-solving Word-list delayed recall
Varanese et al. [52]	Apathy	23 PD with apathy 25 PD without apathy	AES	Executive functions Memory	WCST Digit span CVLT	Set-shifting Working memory Word-list delayed recall
Moretti et al. [47]	Apathy	103 PD	NPI and AES	Executive functions	Letter Fluency Test Stroop test FAB	Verbal fluency Response inhibition Set-shifting
Bogdanova & Cronin-Golomb [57]	Apathy	22 PD	AES	Attention Executive functions Visuospatial Language Memory	Visual symbol search test TMT Letter fluency test RCPM CVLT	Attention Visuospatial
Robert et al. [67]	Apathy	45 PD	AES	Executive functions	Stroop test TMT WCST Letter and category fluency tests	No correlation
Robert et al. [66]	Apathy	36 PD	AES	Emotional facial recognition	EFR Task	Emotional facial recognition
Santangelo et al. [69]	Apathy	62 PD	AES	Memory Frontal functions Visuospatial	Rey's 15-word test Stroop test Constructional apraxia task BJLOT	Frontal functions Visuospatial
Buelow et al. [68]	Apathy	24 PD	Frontal systems behaviour scale	Decision making	Iowa gambling task	Decision making

NPSS: neuropsychiatric symptoms, AES: Apathy Evaluation Scale, NPI: Neuropsychiatric Inventory, LARS: Lille Apathy Rating Scale, MMSE: Mini Mental State Examination, CAMCOG: Cambridge Cognitive Examination, WCST: Wisconsin Card Sorting Test, CVLT: California Verbal Learning Test, TMT: Trail Making Test, COWAT: Controlled Oral Word Association Test, RCPM: Revan's Coloured Progressive Matrices, Scale, FAB: Frontal Assessment Battery, HVLT-R: Hopkins Verbal Learning Test Revised, EFR: Emotional Facial Recognition, BJLOT: Benton Judgment Line Orientation Test.

duration was 8.4 years and they were treated with levodopa), apathy scores significantly correlated with scores on non-verbal tasks of e.g. executive function, assessed by the TMT (part B) and attention, measured by the visual symbol search test [57]. Robert and others [66] reported that apathy scores were negatively correlated with emotional facial recognition scores in patients with PD. However, Robert et al. [67] found that apathy did not correlate with executive functions (assessed by the Wisconsin card sorting test, TMT, category and letter fluency tests and the Stroop test) in non-demented PD patients. Other studies have reported an association between apathy and global cognitive impairment (measured by the MMSE and the Cambridge Examination for Mental Disorders of the Elderly part B) in PD patients [46,50]. More recently published papers have found that apathetic PD patients had lower scores on tasks of frontal functions (evaluated by the Frontal Systems Behaviour Scale and the Stroop test) [68,69] and visuospatial functions (assessed by the Constructional Apraxia Task and the Benton Judgment of Lines Orientation Task) [69] when compared to non-apathetic PD patients.

In the literature, studies of apathy and cognitive abilities in PD patients did not take PD severity into account. In other words, previous studies have not explored the association between apathy and cognitive skills in the early stages of PD, but they have taken a broad definition of the disease and included patients at different severity levels. Further, earlier studies have included a limited number of participants or used general cognitive measurements which do not assess a broader range of cognitive domains. In patients with PD, the development of NPS has been frequently linked to the use of antiparkinsonian treatments but not to dementia [70,71]. There are several pieces of evidence which support the hypothesis that cognitive impairments and dementia are a consequence of the development of NPS in general and apathy in particular [14,41,43–45,47–53,72]. For instance, a recent study [16] explored the frequency of NPS in three groups of patients with PD: patients without

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Table 3
Summary of articles included in the review (Cognitive performance in PD with Hallucinations, ICDs and anxiety).

Authors	NPSS	Number of participants	NPSS assessments	Cognitive domain targeted	Cognitive Tests	Impaired cognitive performance
Grossi et al. [73]	Hallucinations	9 PD with VH 2 PD with auditory hallucination 3 PD with both types of hallucinations 34 PD without hallucinations	DSM-IV	Executive functions Learning Memory Abstract thinking	Letter and category fluency tests Rey's 15-word test RCPM	Verbal fluency Word-list immediate recall
Ramirez-Ruiz et al. [77]	VH	20 PD with VH 20 PD without VH	DSM-IV	Global cognitive ability Memory Spatial functions	MMSE WRMF BFRT BVFDT	Visual memory Visuoperceptive–visuospatial 45% developed dementia after one year
Ozer et al. [76]	VH	33 PD with VH 30 PD without VH	Unified Parkinson's disease Rating Scale	Global cognitive ability Memory Frontal functions	Short test of mental status Stroop test Category fluency test Clock drawing test WCST BJLOT BFRT	Global cognitive ability Verbal fluency Set-shifting Response inhibition Verbal memory
Bronnick et la. [74]	VH	86 PD with dementia	NPI	Executive functions Working memory Visuospatial Attention	D-KEFS Serial7s task from MMSE Visual construction task subtest of ADAS-Cog Go/no-go test	Response processes
Shin et al. [78]	VH	46 PD with VH 64 PD without VH	NPI	Executive functions Memory	Stroop test Rey complex figure test	Set-shifting Response inhibition Delayed recall
Hepp et al. [75]	VH	31 PD with VH 31 PD without VH	Scales for outcome in Parkinson disease	Executive functions Memory	TMT Rey 15-word test	Visuo–motor speed Immediate recall
Santangelo et al. [87]	ICDs	15 PD with ICDs 15 PD without ICDs	DSM-IV	Frontal functions Memory Abstract thinking	FAB TMT Letter and category fluency tests WCST Rey complex figure test RCPM	Cognitive flexibility Set-shifting Abstract thinking Delayed recall Spatial planning
Djamshidian et al. [86]	ICDs	18 PD with ICDs 12 PD without ICDs	DSM-IV	Memory Learning	Digit span Associative learning task	Working memory
Vitale et al. [88]	ICDs	45 PD with ICDs	Minnesota impulsive disorders interview	Frontal and executive functions Memory	TMT WCST Stroop test Rey complex figure-copying task Rey 15-word test	Spatial planning Set-shifting Cognitive flexibility Inhibitory control Immediate and delayed recall
Biundo et al. [85]	ICDs	33 PD with ICDs 24 PD without ICDs	Minnesota impulsive disorders interview	Global cognitive abilities Memory visuospatial Abstract reasoning attention	MMSE TMT Rey complex figure test Similarities Task RCPM Digit span	Set-shifting General lobe function
Voon et al. [89]	ICDs	14 PD with ICDs 14 PD without ICDs	DSM-IV	Spatial working memory Set-shifting	CANTB Intra-extradimensional set shifting task	Spatial working memory
Foster et al. [90]	Anxiety	59 PD	State-trait anxiety inventory	Memory	Digit span	Working memory
Bogdanova & Cronin-Golomb [57]	Anxiety	22 PD	Beck anxiety inventory	Executive functions Attention Visuospatial Language Memory	COWAT-FAS TMT Digit span RCPM Boston naming test CVLT	Verbal fluency Language Immediate and delayed recall

NPSS: neuropsychiatric symptoms, VH: Visual Hallucination, ICDs: Impulse Control Disorders, DSM: Diagnostic and Statistical Manual of Mental Disorders, NPI: Neuropsychiatric Inventory, RCPM: Revan's Coloured Progressive Matrices, MMSE: Mini Mental State Examination, WRMF: Warrington Recognition Memory for Faces, BFRT: Benton Facial Recognition Test, BVFDT: Benton Visual Form Discrimination Test, WCST: Wisconsin Card Sorting Test, BJLOT: Benton Judgment Line Orientation Test, D-KEFS: Delis–Kaplan Executive Function System, ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognition, TMT: Trail Making Test, FAB: Frontal Assessment Battery, CANTB: Cambridge Automated Neuropsychological Test Battery, COWAT: Controlled Oral Word Association Test, CVLT: California Verbal Learning Test.

cognitive impairment (PD-NC, n = 54), patients with mild cognitive impairment (PD-MCI, n = 48) and patients with dementia (PDD, n = 25). Patients who showed at least one NPS were 39 (72.2%) in the PD-NC group, 38 (79.2%) in the PD-MCI group and 24 (96%) in the PDD group. Apathy was more frequent in the PD-MCI and PDD groups than the PD-NC group. In this study, apathy was also significantly correlated with factors such as advanced stage of disease and dopamine agonist load and all cognitive measures used in that study (e.g. trail making

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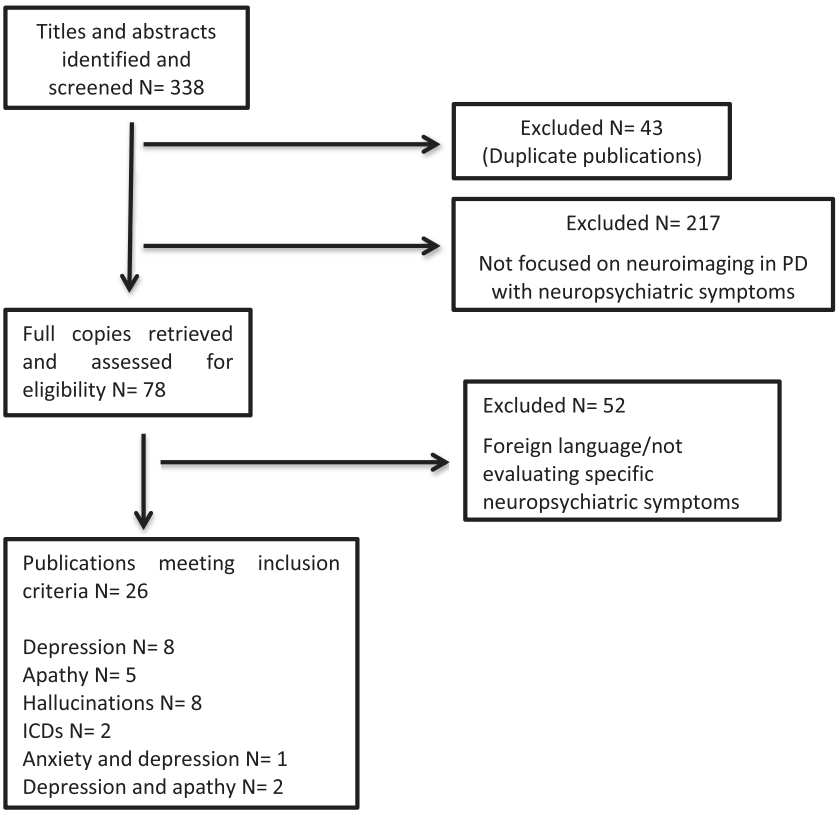

Fig. 2. Flow chart of study selection process (neural correlates of neuropsychiatric symptoms in PD).

test, verbal fluency task, Wisconsin card sorting test, 5-minute recall of 3 words and MMSE) [16].

3.1.3. Psychosis

The most common psychotic symptom in PD is visual hallucination (VH) [73]. Several studies have observed cognitive decline in patients with PD who have VH [73–78] (See Table 3). For example, a study examined the presence of cognitive impairment in non-demented PD patients with VH (mild to moderate disease stages, average disease duration was 6.79 years, average years of PD onset was 60.21 and all patients treated with levodopa). Patients with VH had significantly lower scores relative to patients without VH in global cognitive abilities assessed by the short test of mental status [79], frontal functions, evaluated by the Stroop test [65], category fluency task [64], the clock drawing test [80] and non-verbal memory assessed by the visual reproduction subtest of the Wechsler memory scale [81]. However, there were no significant differences between the two PD subgroups in visual perceptive functions measured by the Benton face recognition test [82], the judgment of line orientation test [83] and one of the frontal functions test which was the Wisconsin card sorting test [84]. These results suggest that PD patients with VH might have deterioration in frontal and memory functions [76]. Moreover, a further study reported that PD patients with VH had cognitive impairment in visual memory tasks (evaluated by the Warrington recognition memory for faces), visuoperceptive and visuospatial functions (assessed by the Benton facial recognition test and the standard drawing and multiple-choice versions of the Benton visual form discrimination test respectively) compared with PD patients without VH [77] (in this study patients had mild to moderate disease stages and were treated with levodopa). A recently published study examined cognitive decline in non-demented PD patients with and without VH (patients were treated with levodopa, dopamine agonist and anticholinergic medications). Results revealed that patients with VH performed significantly lower than patients without this symptom on tasks of executive function (measured by the Stroop test) and delayed recall which was evaluated by the Rey complex figure test [78].

3.1.4. Impulse control disorders

Few studies have examined cognitive functioning in PD patients with ICDs. The cognitive domain that appears to be mostly impaired in PD patients with ICDs is executive functioning [85–89] (See Table 3). Biundo and others [85] reported executive dysfunction in PD patients with ICDs (average disease duration was 8.81 years, age at onset was 53.18 and all patients treated with dopamine agonist). This cognitive impairment specifically was found in general frontal lobe function (detected by the TMT part B) and in shifting abilities as measured by the TMT part B minus part A score [85]. Furthermore, other studies have reported memory impairment in PD patients with ICDs, particularly, in spatial working memory tasks assessed by the Cambridge automated neuropsychological test battery [89] (in this study the average age at PD onset was 53.49 and patients were treated with levodopa and a dopamine agonist), short-term memory and working memory as measured by digit span forward and backward [86].

3.1.5. Anxiety

Only two studies have investigated the relationship between anxiety and cognitive functions in PD patients [57,90] (See Table 3). The first study reported that left-lateralized PD patients with anxiety performed significantly worse than right-lateralized PD patients with anxiety on working memory tasks, i.e. the digit span backward subtest of the Wechsler memory scale [90]. The second study reported that in PD patients with right-side onset, anxiety scores were significantly correlated with verbal deficits including verbal fluency (assessed by the controlled word association test-FAS), language and memory (evaluated by the Boston naming test and the California verbal learning test respectively) [57].

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Table 4
Summary of articles included in the review (Neuroanatomical of PD with neuropsychiatric symptoms).

Authors	NPSS	Number of participants	Imaging technique	Affected brain area
Ring et al. [99]	Depression	10 PD with depression 10 PD without depression	PET	Bilateral medial frontal cortex and anterior cingulate cortex
Remy et al. [98]	Depression	20 PD	PET	Bilateral locus coeruleus and limbic system
Matsui et al. [96]	Depression	23 PD with depression 27 PD without depression	diffusion tensor MRI (ROI)	Bilateral anterior cingulate bundle
Feldmann et al. [92]	Depression	23 PD with depression 27 PD without depression	VBM	Left inferior orbito-frontal gyrus, bilateral rectal gyrus and right superior temporal pole
Cardoso et al. [91]	Depression	20 PD with depression 18 PD without depression	fMRI ROI	Left mediodorsal nucleus of the thalamus and medial prefrontal cortex
Kostic et al. [94]	Depression	16 PD with depression 24 PD without depression	VBM	Right posterior cingulate cortex, right inferior temporal gyrus and right hippocampus
Li et al. [95]	Depression	14 PD with depression 18 PD without depression	diffusion tensor MRI (ROI)	Bilateral mediodorsal thalamus
Petrovic et al. [97]	Depression	34 PD with depression 25 PD without depression	MRI (White matter hyperintesities)	No differences
Huang et al. [93]	Depression Apathy Anxiety	26 PD	PET (ROI)	Bilateral amygdala Bilateral anterior cingulate and orbitofrontal lobe Bilateral caudate nucleus
Sheng et al. [100]	Depression	20 PD with depression 21 PD without depression	Resting-state fMRI	Left middle frontal gyrus and right inferior frontal gyrus, bilateral amygdala and lingual gyrus
Isella et al. [45]	Apathy	30 PD	Morphometric MRI	No correlation
Le Jeune et al. [104]	Apathy	12 PD	PET	Right middle/inferior frontal gyrus and bilateral posterior cingulate gyrus
Reijnders et al. [50]	Apathy	55 PD	VBM	Left precentral gyrus, bilateral inferior parietal gyrus, inferior frontal gyrus, insula and right posterior cingulate gyrus
Skidmore et al. [101]	Apathy	22 PD	fMRI	Right middle orbital-frontal gyrus, bilateral subgenual cingulate, left supplementary motor regions, left inferior parietal lobule and fusiform gyrus
	Depression			Right subgenual cingulate, bilateral cuneus, right geniculate and mesial frontal gyrus
Robert et al. [67]	Apathy	45 PD	PET	Right inferior/middle frontal gyrus, cuneus, insula and bilateral cerebellum
Robert et al. [66]	Apathy	36 PD	PET	Left posterior cingulate
Nagano-Saito et al. [109]	VH	11 PD with VH 8 PD without VH	PET	Left superior frontal gyrus
Oishi et al. [110]	VH	24 PD with VH 41 PD without VH	SPECT	Right superior/middle temporal gyri and fusiform gyrus
Ramirez-Ruiz et al. [77]	VH	10 PD with VH 10 PD without VH	fMRI	Right inferior/middle/superior frontal and anterior cingulate gyrus
Ibarretxe-Bilbao et al. [108]	VH	44 PD	VBM (ROI)	Hippocampus (Anterior regions)
Shin et al. [78]	VH	46 PD with VH 64 PD without VH	VBM	Right orbitofrontal, left temporal and thalamic areas
Watanabe et al. [113]	VH	13 PD with VH 13 PD without VH	VBM	Bilateral dorsolateral prefrontal cortex, left rostral prefrontal cortex, left cingulate cortex, bilateral primary and secondary visual cortex and parahippocampal
Pagonabarraga et al. [111]	VH	17 PD with VH 29 PD without VH	VBM	Bilateral inferior frontal cortex precuneus, cerebellum
Gama et al. [107]	VH	39 PD	VBM	Left opercula frontal gyrus Left superior frontal gyrus
Steeves et al. [114]	ICDs	7 PD with ICDs 7 PD without ICDs	PET	Ventral striatum
Biundo et al. [85]	ICDs	33 PD with ICDs 24 PD without ICDs	VBM	Bilateral middle/superior frontal gyrus

NPSS: neuropsychiatric symptoms, VH: Visual Hallucination, ICDs: Impulse Control Disorders, MRI: Magnetic Resonance Imaging, VBM: Voxel-Based Morphometry, SPECT: Single Photon Emission Computed Tomography, PET: Positron Emission Tomography, fMRI: functional Magnetic Resonance Imaging, ROI: Region of Interest.

3.2. Neuroanatomical correlates of neuropsychiatric symptoms in PD

3.2.1. Depression

We found 11 imaging studies that have explored the neural bases of PD patients with and without depression using different imaging techniques [91–101] (See Table 4). Among these studies, there is only one study that found no differences in brain regions between PD patients with and without depression [97] (in this study patients had mild to severe disease stages, average disease duration was 4.9 years and age at onset was 62.6). However, other articles reported brain changes in depressed PD patients. For instance, a recently published PET study reported that in patients with PD, depression scores (as assessed by the Beck depression inventory) correlated with increased brain metabolism in the amygdala [93]. Other studies have emphasised the important role of the dorsomedial prefrontal cortex in a similar group of patients [99]. A PET study found that PD patients with depression had decreased cerebral blood flow in the frontal cortex and in the anterior cingulate cortex when compared with PD patients without depression and controls [99]. Two VBM studies reported that depressed PD patients had lower grey matter density in the frontal, temporal cortex [92] (in this study patients had moderate disease stage, their average disease duration was 9.9 years and they were treated with levodopa), in the posterior cingulate cortex and the hippocampus [94] (this study included patients with mild to moderate disease stages, average disease duration was

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6 years and they were treated with levodopa). Sheng et al. [100] found that functional connectivity was decreased within the prefrontal-limbic system and increased in the prefrontal cortex and lingual gyrus in PD patients with depression.

A limited number of studies have investigated white matter volume in PD patients with depression. These studies revealed that PD patients with depression had white matter reductions in the right anterior cingulate bundle, inferior orbitofrontal regions and in the left inferior parietal lobe [94], the frontal lobe bilaterally, possibly representing dysfunction in bilateral anterior cingulate bundles [96], and the mediodorsal nucleus of the thalamus bilaterally [95].

In summary, two VBM studies have explored the neural correlates of depression in PD patients [92,94], but these studies have various limitations. For instance, in the Feldmann et al. study, PD patients were in the moderate stage of the disease [130]. The exploration of depression in patients with early stage of PD may allow for more effective diagnosis and intervention. In addition, the earlier studies did not covariate for total intracranial volume, which might have contributed to the results of grey matter reduction. Furthermore, the authors relied on reports of previous episodes of other neuropsychiatric symptoms in order to exclude patients who had these symptoms. Finally, the Kostic et al. study included PD patients in the mild to moderate stages, a very small sample size and included 8 patients who were treated with antidepressants [94]. It has been reported that antidepressant medications activate specific brain regions which may influence the results of neuroimaging studies that investigate depressive symptoms [102]. For instance, a meta-analysis [103] of fMRI and PET studies has shown that antidepressants in major depression increase the activation of dorsolateral, dorsomedial and ventrolateral prefrontal cortex, whereas the activation was decreased in the amygdala, hippocampus, parahippocampal areas, ventral anterior cingulate cortex and orbitofrontal cortex. Therefore, it seems that the exclusion of patients who take antidepressants is highly recommended in functional neuroimaging studies in order to have more precise results.

3.2.2. Apathy

Despite the fact that apathy is probably the most frequently observed neuropsychiatric symptom in PD patients, the neural bases of apathy in PD patients remain unclear. We found 7 studies that have investigated the underlying mechanism of apathy in PD using a variety of imaging techniques [45,50,66,67,93,101,104] (See Table 4). A PET study investigated apathy in non-demented PD patients after deep brain stimulation of the subthalamic nucleus (average disease duration at surgery was 11.2 years) using the apathy evaluation scale [105]. In this study, positive correlations were identified between apathy scores and glucose metabolism in the frontal lobe, whereas apathy scores were negatively correlated with glucose metabolism in the posterior cingulate gyrus and the frontal lobe [104]. A VBM study has shown evidence that in PD low grey matter density in many cortical brain regions within the frontal, parietal, cingulate cortex correlated with high apathy scores [50]. An fMRI study investigated the specific characteristics of apathy, depression, and motor progression in the resting state of PD patients using the amplitude of the low frequency fluctuation (ALFF). Higher apathy scores were associated with increased normalized ALFF signal in the frontal and in the cingulate cortex bilaterally. Conversely, higher apathy scores were correlated with decreased activity in the supplementary motor region, the parietal lobule and the fusiform gyrus. Severity of depression was correlated with increased normalized ALFF signal in the cingulate, the cuneus, the lateral geniculate nucleus and the mesial frontal gyrus [101].

The involvement of the frontal and cingulate cortex has been constantly observed in PD patients with apathy. More recent PET studies have supported this view; for instance, Robert el al. [67] found that apathy scores correlated positively with cerebral metabolism in the inferior/middle frontal gyrus, cuneus and the insula. Negative correlations were identified between apathy scores and cerebral metabolism in the bilateral cerebellum, particularly the inferior semilunar lobule [67]. A more recent PET study in PD patients showed that apathy scores correlated with increased metabolism in the anterior cingulate and orbitofrontal lobe bilaterally [93]. Robert et al. [66] also reported increased metabolism within the posterior cingulate cortex in apathetic patients with PD. However, a different study did not identify any specific measure of frontotemporal atrophy correlating with the presence or severity of apathy [45].

To our knowledge, none of the earlier studies has investigated white matter changes in patients with PD who have apathy. However, in other neurological disorders such as Alzheimer's disease this point has been studied with one study reporting that apathetic AD patients had a significantly greater amount of frontal white matter hyperintensities than non-apathetic AD patients [106].

It can be noticed from the above review that the association between apathy and white matter volume in PD has not yet been explored. In addition, only one VBM study has investigated grey matter volume in PD with apathy but this study had various limitations such as the inclusion of patients with only mild apathy scores and the use of only a correlational analysis design. Indeed, there is evidence that apathy is associated with atrophy of the frontal and cingulate cortex in PD [50,104].

3.2.3. Psychosis

Most of the earlier imaging studies that attempted to explore psychosis in patients with PD focused on the study of visual hallucination [78,107–113] (See Table 4). Previous reports suggest that VH in PD patients can be correlated either with cortical or subcortical atrophy [113]. Specifically, VH was associated with dysfunction of frontal lobe [78,109,111–113], temporal lobe [78,110], cingulate cortex [112,113], hippocampus [112], parahippocampal, primary and secondary visual cortex [113], thalamus [78], precuneus and cerebellum [111]. A VBM study investigated grey and white matter alterations in PD patients with VH (patients had mild to moderate disease stages, average disease duration was 10 years, average age at PD onset 53.6 and they were treated with levodopa) [113]. This study reported grey matter reduction in the prefrontal cortex, cingulate cortex and visual association areas in PD patients with VH. The same group of patients showed white matter reduction in the parahippocampal gyrus, posterior cingulate gyrus, lingual gyrus and middle occipital gyrus when compared with PD patients without VH. However, this study included a small number of patients. A further study has reported grey matter reduction in the left frontal areas in patients with PD who have developed VH when compared with those patients without VH [107] (in this study the average disease duration for patients was 5.3 years and average age at PD onset was 63.1).

3.2.4. Impulse control disorders

We found only two imaging studies that have investigated ICDs in PD patients [85,114] (See Table 4). The first study reported decreases in the binding potential of a dopaminergic tracer in the ventral striatum in PD patients with pathological gambling [114] (this study included patients with mild to moderate disease stages and their average disease duration was 7.4 years). Additionally, a VBM study examined brain volume changes in PD patients with and without ICDs and healthy controls. The Minnesota impulsive disorders interview was used to assess ICDs. When compared with controls, PD patients (with and without ICDs), had a significantly lower grey matter volume in frontal lobe [85].

3.2.5. Anxiety

Only one recent imaging study has examined the association between anxiety and brain metabolism changes in patients with PD (see Table 4). Huang et al. [93] studied the correlation between anxiety scores (as assessed by the Beck anxiety inventory) [115] and brain metabolism in non-demented patients with PD. This study used a region of interest (ROI) approach to explore PD-related regions e.g. the motor

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cortex, cingulate cortex, occipital lobe, frontal cortex, cerebellum, limbic system and temporoparietal association cortex. The anxiety scores correlated with decreased metabolism in the caudate nucleus bilaterally [93].

5. Discussion

Most of the prior studies reported differences in cognitive abilities between patients with PD with and without neuropsychiatric symptoms; these findings suggest that the presence of neuropsychiatric symptoms can affect cognitive skills in this patient population. Particularly, significant differences were detected on tests that mainly assess executive functioning (e.g. inhibitory control and working memory), a pattern of finding which fits the cognitive profile of patients with frontal lobe dysfunction. Moreover, the association between neuropsychiatric symptoms and executive dysfunction has been reported in non-demented PD patients, [19,116], again, adding to the conclusion that neuropsychiatric symptoms in PD may be associated with specific regional frontal lobe dysfunction and might not necessarily be a consequence of overall cognitive impairment.

In general, there are three core types of executive functions which seem to be repeatedly involved and these are inhibitory control, working memory and cognitive flexibility [117]. Thus perhaps, the inability to perform well on the tasks that assess executive functions in PD routes from poor working memory and a lack of control over the stimuli presented to them in the context of prefrontal cortex damage. Furthermore, the atrophy observed within the frontal circuits contributes to the manifestation of neuropsychiatric symptoms in PD, leading to poor self-control and a weak attention span (including both behavioural and cognitive abnormalities).

In line with the above, there have been similar patterns of association observed in neurodegeneration related to AD type pathology in experiments in which patients with MCI with neuropsychiatric symptoms have also been studied with a comprehensive battery of neuropsychological tests. For instance, Rosenberg and colleagues [118] found that the presence of executive dysfunction in MCI was associated with greater severity of neuropsychiatric symptoms as assessed by the NPI, specifically depression, anxiety, agitation, apathy, disinhibition, irritability, and sleep disturbance. This finding is also supported by another study by Ellison et al. [119] who reported that the most frequent symptoms were depression/dysphoria, apathy, anxiety, irritability/lability and nighttime abnormal behaviour in MCI. Another study [120] showed that MCI patients with a high number of neuropsychiatric symptoms (four or more) are more likely than patients with fewer symptoms (up to three) to have the amnestic form of MCI, which most likely reflects the presence of neurodegeneration leading to AD dementia. Amnestic MCI patients with more neuropsychiatric symptoms had a greater risk of developing dementia than those with fewer symptoms.

A systematic review study of MCI patients indicated that the prevalence of neuropsychiatric symptoms ranged from 35% to 75% with the most common being depression, apathy, anxiety and irritability [120–122]. These studies also reported that MCI patients with behavioural disturbances are more likely to develop AD than patients without these features. Furthermore, Trivedi et al. [123] reported that neuropsychiatric symptoms (as measured by the NPI) were significantly more severe and frequent in patients with MCI than in healthy participants, and demented patients had significantly more neuropsychiatric problems than MCI and healthy groups. Other studies have shown that there was a negative association between frequency of neuropsychiatric symptoms and MMSE scores in patients with MCI [120,122].

In view of the findings of the current review and the MCI studies, it can be said that the development of neuropsychiatric symptoms goes in parallel with cognitive decline and should be thoroughly assessed in patients with cognitive impairment (independently of the underlying neurodegenerative aetiology, i.e. whether due to PD or AD). These findings also raise the question of whether treatment of neuropsychiatric symptoms in PD or MCI (due to AD) might prevent or delay progression to dementia. Further investigations are required to address this point.

Despite the cognitive investigations were done independently from the imaging studies, a speculative attempt can be made to integrate some of the findings from both types of study. For instance, Starkstein et al. [28] found that depressed PD patients had executive dysfunction which was detected by the TMT. This result may reflect less brain activation in the middle frontal gyrus, a finding that was reported in the Sheng et al. [100] study. This speculation is also supported by an fMRI study that found brain activation in the middle frontal gyrus in healthy participants while performing the TMT [124]. In addition, the low scores on the letter fluency test found in depressed PD patients in the cognitive studies [31,33] could be explained by brain atrophy in the anterior cingulate gyrus [79,80]. The letter fluency task requires the participant to initiate extensive searches for suitable words. Also for this task, evidence from fMRI studies is helpful as an association between the anterior cingulate cortex and letter fluency performance has been repeatedly reported in healthy participants [125–127].

This review of the literature illustrates studies that have investigated the association between cognitive abilities and neuropsychiatric symptoms in patients with PD. However, these studies did not control for the presence of other neuropsychiatric symptoms when they investigated a specific symptom in patients with this disease. Prior research has provided evidence that neuropsychiatric symptoms in Parkinson's disease can manifest either as independent isolated symptoms or as multiple co-occurring symptoms. In addition, there are some methodological issues that have been raised following studies that examined specific neuropsychiatric symptoms. For instance, when examining cognitive decline within a group of patients with a particular neuropsychiatric symptom, it is very important to exclude patients who experience multiple symptoms. This approach will allow a better understanding of the possible cognitive correlates when breaking down the results for each specific symptom. However, most previous work did not take this issue into account. Another point is that certain studies assess only global cognitive abilities or limited cognitive domains. Additionally, prior investigations did not focus on the early stages of PD when examining these variables. Similar methodological issues have been found in some published studies that have explored the brain regions that may correlate with specific neuropsychiatric symptoms.

Future studies should take all the limitations highlighted above into account and especially study neuropsychiatric symptoms in patients at a much earlier stage of the disease. It would also be an advance if the presence of symptoms were ascertained by using an instrument which can detect also the presence of other concomitant neuropsychiatric symptoms. An instrument such as the Neuropsychiatric Inventory [128] for example (or others with similar structure) would allow the exclusion of other co-occurring symptoms when exploring a particular feature. In addition, in most of the available studies a limited range of cognitive abilities was assessed. The use of an extensive neuropsychological battery to explore multiple cognitive domains could provide a clearer picture of the cognitive skills which might have deteriorated in non-demented PD patients who develop a specific neuropsychiatric symptom or a given set of symptoms. Furthermore, cognitive and neuroimaging studies of anxiety in patients with PD are limited. Only two studies have examined the cognitive correlates of anxiety in PD [57, 90] but neither of them compared patients with anxiety versus patients without any neuropsychiatric symptoms or healthy controls. The underlying neurobiological mechanisms of anxiety in PD, therefore, have yet to be explored, which is something that could add a further dimension to the investigation and clarification of the causes of neuropsychiatric symptoms in PD.

The overall underlying mechanisms of neuropsychiatric symptoms in PD are still unclear. Although there are several published studies which have investigated the neural correlates of neuropsychiatric symptoms using different approaches, little is known about the structural brain areas that may associate with these symptoms. It has been

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reported that a VBM approach offers a suitable way to explore grey and white matter volume changes as it has been championed for its powerful unbiased hypothesis testing approach across the whole brain [129]. Finally, a combination of both neuropsychological and more advanced imaging techniques (i.e. diffusion tensor imaging and resting state fMRI) in exploring neuropsychiatric symptoms in the same cohort of patients with PD might provide a better understanding of both the cognitive and the neural breakdowns associated with the genesis of neuropsychiatric symptoms in the early stages of PD.

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