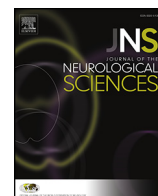




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Review article

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

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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.

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Contents

1.	Introduction	0
2.	Method	0
3.	Results	0
3.1.	Cognitive correlates of neuropsychiatric symptoms in PD	0
3.1.1.	Depression	0
3.1.2.	Apathy	0
3.1.3.	Psychosis	0
3.1.4.	Impulse control disorders	0
3.1.5.	Anxiety	0
3.2.	Neuroanatomical correlates of neuropsychiatric symptoms in PD	0
3.2.1.	Depression	0
3.2.2.	Apathy	0
3.2.3.	Psychosis	0
3.2.4.	Impulse control disorders	0
3.2.5.	Anxiety	0

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E-mail address: a.venneri@sheffield.ac.uk (A. Venneri).

5. Discussion	0
Acknowledgements	0
References	0

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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