Altered awareness of motor symptoms in Parkinson's disease and Dementia with Lewy Bodies: a systematic review

Title:

Altered awareness of motor symptoms in Parkinson's disease and Dementia with Lewy Bodies: a systematic review

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Abstract

Objectives: Altered awareness of motor symptoms is reported in people with Parkinson's disease and Dementia with Lewy Bodies, and may adversely affect quality of life and medication concordance. How symptom awareness is influenced by motor and cognitive disease severity, age and medication use is not fully understood. We carried out a systematic review of the literature on motor symptom awareness in Parkinson's disease and Dementia with Lewy Bodies.

Methods: Pubmed and Wed of Science were searched for relevant articles published in or prior to March 2019. Data regarding participant demographics, diagnosis, cognitive status, method of assessing awareness and study findings were extracted from relevant publications.

Results: 16 relevant publications were identified. Motor symptom awareness appears to decline over the course of Parkinson's disease. Imaging studies implicate the prefrontal cortex, with different mechanisms involved in hypokinesia and dyskinesia awareness. The hypothesis that people with right hemisphere based disease would have more severely reduced awareness is only weakly supported. Most studies focused on cognitively intact individuals, and on awareness of dyskinesia rather than hypokinesia.

Conclusions: Whilst reduced awareness of dyskinesia and to a lesser extent hypokinesia is common, there is a lack of longitudinal data on how awareness changes over time, and how it interacts with global cognitive changes. Motor symptom awareness in Dementia with Lewy Bodies is understudied. Future studies of symptom awareness should include robust assessment of overall cognitive functioning, and use a longitudinal design to elucidate how awareness changes over time.

Keywords:

Symptom awareness	Parkinson's disease
Insight	Parkinson's disease dementia
Anosognosia	Dementia with Lewy bodies
Metacognition	

Key points:

Reduced awareness of motor symptoms is a common phenomenon in Parkinson's disease.

Impaired monitoring of planned versus executed movements may contribute to reduced dyskinesia awareness in Parkinson's disease.

Dopaminergic medications impact on motor symptom awareness in Parkinson's disease.

The prefrontal cortex is involved in motor symptom awareness in Parkinson's disease, with differing networks implicated in dyskinesia and hypokinesia awareness.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder, which encompasses a range of motor and non-motor symptoms[1]. PD is associated with multiple neuroanatomical and neurotransmitter abnormalities which can impact on awareness of symptoms across a range of modalities[2–5]. Impaired symptom awareness, also referred to as anosognosia or loss of insight, can be conceptualised as the inability to accurately gauge one's level of functioning or degree of symptomatology[6,7]. The term 'metacognition' is used in reference to the process of 'thinking about thinking' – that is, to be aware of one's own level of functioning in different cognitive and physical domains[8,9]. Awareness of one's memory functioning is termed 'meta-memory'. Loss of insight may therefore also be referred to as impaired metacognition. Individuals may be unaware of how their motor symptoms affect personal safety and how they assess risk (for example, whether or not they can safely drive), or the degree of side effects such as dyskinesias[10–13]. Altered symptom awareness affects healthcare seeking behaviour and medication concordance[12,14]. Untreated motor and non-motor symptoms can have a negative impact upon the quality of life of the individual and contribute to carer strain[15–17].

Improving our understanding of insight in PD is particularly relevant given the projected future increases in the number of people affected by PD worldwide[18]. Dementia is a frequent complication of PD, with over 70% of people diagnosed with PD developing Parkinson's Disease Dementia (PDD) over time[19]. Clinically and pathologically, PDD is closely related to Dementia with Lewy Bodies (DLB), with the two conditions being distinguished by the sequence and severity in which motor and cognitive symptoms occur[20,21]. Clinically significant altered awareness is a feature of multiple different forms of dementia, including PDD and DLB[2,6]. The impact of DLB on symptom awareness is a particularly understudied area. Loss of symptom awareness is therefore an important topic, and one which has received increasing research attention in recent years.

Work with healthy control subjects and people with Alzheimer's disease (AD) implicates the cingulate cortex, insula and prefrontal cortex (PFC) as critical areas for symptom awareness[22–24]. Loss of awareness of memory, social and behavioural functioning in AD has been strongly associated with atrophy of the medial temporal lobe (MTL)[25], but it is unclear if different aspects of awareness (for example awareness of motor symptoms vs awareness of memory impairment) are supported by different brain networks. The MTL and medial PFC are strongly interconnected, as are the medial PFC and the anterior cingulate cortex (ACC). Additionally, a network spanning the posterior parietal cortex, supplementary motor area and premotor cortex is proposed to support the conscious experience of voluntary motor actions[26]. A particular role for the right hemisphere (and by extension the right basal ganglia) has been inferred from the experience of anosognosia in stroke patients being particularly right hemisphere related[27].

Regional brain atrophy accumulates over time in PD, affecting the frontal lobes, medial temporal lobes, and hippocampus[28]. Parallels are seen between the severity and distribution of atrophy and cognitive performance[29]. Atrophy is most widespread and severe in PDD, although relative

preservation of the MTL is seen in comparison with AD[28]. The neural regions and networks sub-serving conscious recognition of symptoms are therefore at risk in PD. Additional potential for malfunctioning symptom awareness comes from changes to neurotransmitter systems in PD[30,31].

This systematic review discusses the findings from studies of awareness of motor symptoms in PD and DLB, including the impact of dopaminergic medication and global cognitive status. We provide a critical analysis of current knowledge and propose future research directions.

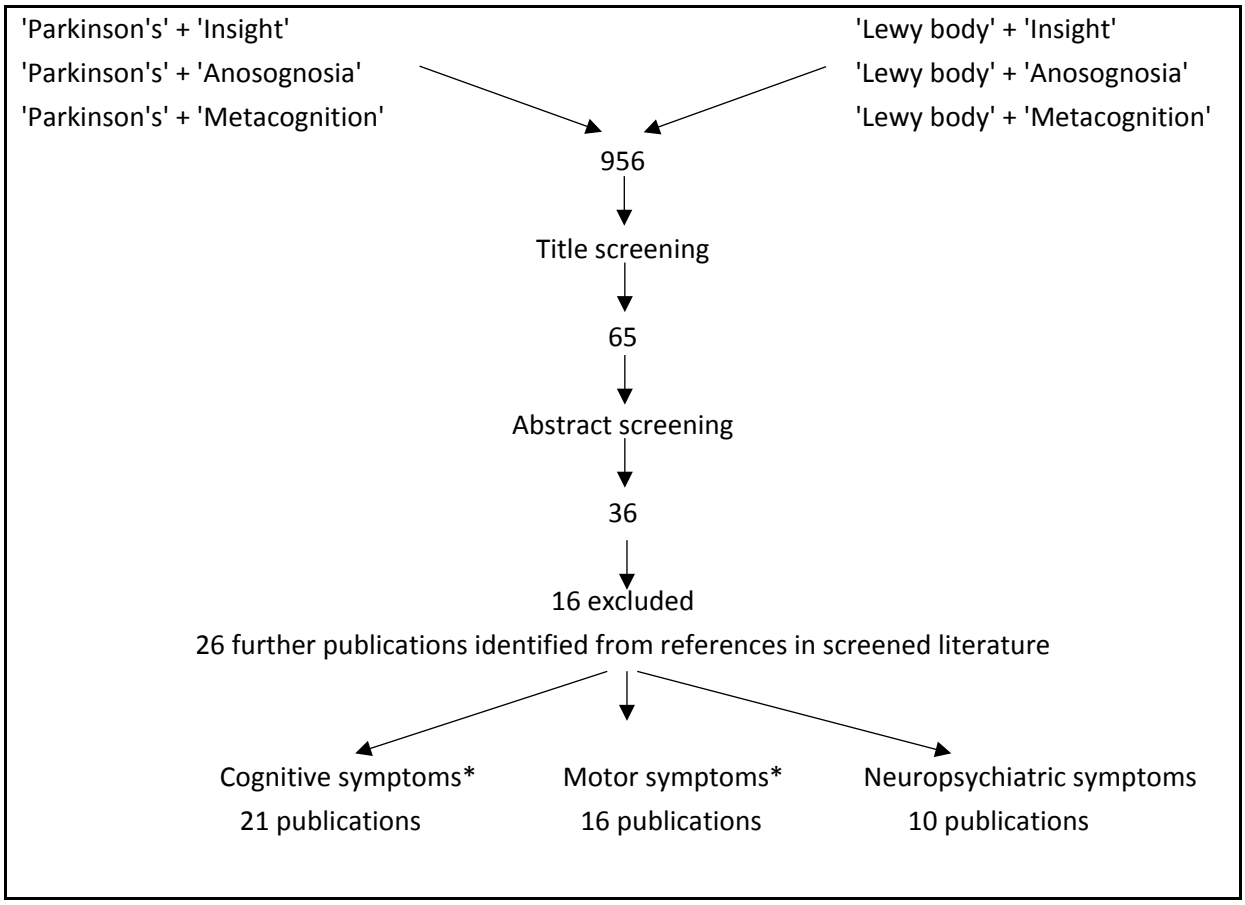
2. Methods

A systemic review was undertaken of the literature investigating altered insight in PD and DLB, across motor symptoms, neuropsychiatric and cognitive symptoms. The findings for awareness of motor symptoms are reported in the current publication. In order to capture the extent of the literature a range of search terms were used. Either 'Parkinson's' or 'Lewy body' were used as a term to denote the disease of interest, combined with either 'insight', 'anosognosia' or 'metacognition' to denote the cognitive area of interest. The term ‘awareness’ was not used as a search term due to the high frequency of off-topic usage in the English language. Searches were conducted between January and March 2019, limited to papers published in English and dealing with humans. Pubmed and Wed of Science searches were conducted. Duplicates were excluded, followed by screening by title, then abstract. Relevant publications detailing investigations of insight in PD or DLB were then selected after a full review of the text. Additional relevant publications were identified from these selected publications. Screening of publications was undertaken by one author (CP).

Conference abstracts were included if these were indexed for MEDLINE and included essential study data such as group sizes and results data. Data was then extracted following a standardised format, capturing group sizes and diagnosis, baseline group age and cognitive functioning, the nature of the measure of symptom awareness, and study findings. The medication status during assessment was dichotomised to being ON medication, referring to participants being within the therapeutic window of their dopaminergic medication, or OFF medication, referring to participants being outwith the therapeutic phase of their medication.

Variable terminology is in use in the literature. Terms commonly used are symptom 'awareness', or 'insight' into symptoms, alongside 'anosognosia' and 'metacognition' or 'meta-memory'. Whilst different authors use different precise definitions, broadly they refer to whether or not an individual is consciously aware of and able to accurately report a particular symptom (such as dyskinesias) or ability (such as memory function). This review will use the term 'awareness' to refer to whether subjects can accurately report the presence, absence and severity of symptoms or level of ability or impairment.

Box 1. Search strategy



* 1 publication[32] reported both cognitive and motor findings therefore appears in both the 'cognitive' and 'motor' groups.

3. Results

3.1 Literature search

A total of 956 publications were identified from the initial search (Box 1). After screening of titles and abstracts, 20 relevant publications were retained. Hand screening of the reference lists from these publications identified a further 26 relevant publications. These were then sub-divided according to whether they reported the investigation of insight into motor symptoms (16 publications, Table 1), or neuropsychiatric and cognitive symptoms (reported elsewhere). 1 publication[32] reported both motor and cognitive findings. Study methodologies and key findings of each study are shown in Table 2, and an assessment of study quality in Table 3.

3.2 Participant groups

Participant group details are given in Table 1. All 16 studies recruited people with PD from specialist hospital clinics; no studies of motor symptom awareness in DLB were identified. The mean age of participants was typically in the 7th decade, and disease duration was between 4.00 and 13.50 years (disease duration was not stated in 4 studies). The majority of studies actively excluded people with cognitive impairment, typically using a cut off on the Mini-Mental State Examination (MMSE), with the minimum accepted MMSE for study inclusion ranging from of 23.00 to 28.00. Three studies did not report participants' MMSE or Montreal Cognitive Assessment (MoCA) score. Overall the MMSE of study participants with PD (where reported) ranged from 23.40 to 29.23; the majority of studies reported a mean of 27.00 or greater. The number of participants with PD in individual studies ranged from 17 to 104, with a median of 25 PD participants per study (Table 1). Most study groups were small to medium, with only 6 studies containing more than 40 participants with PD. An excess of male participants was seen, with a female:male ratio of 1:1.21.

3.3 Techniques for assessing symptom awareness

All studies used discrepancy scores to rate awareness of motor functioning (Table 2). This technique involves asking the participant to rate their own ability, symptom or performance, and this score is compared to that given by a knowledgeable carer or expert rater. Most studies used a structured questionnaire or semi-structured interview, whilst others asked participants to perform a defined motor task and then record the severity of any motor symptoms they experienced during the task[33]. 10 studies used a physician or study examiner to provide an 'objective' assessment of motor symptoms, whilst 8 used the opinion of a carer or other personal informant (note 1 study used both an examiner and an informant). One study used a modified mirror box task to capture changes to emotions during movement[33]. A modified version of the Wisconsin Card Sorting Test (WCST) was used in 1 study to examine metacognitive basis of altered awareness of dyskinesias.

3.4 Timing of assessments

Of the 16 studies identified, 5 assessed participants whilst ON and OFF dopaminergic medication[34–38] whilst 5 only tested during the ON state, and the remaining 6 studies did not report the medication status of study participants[2,39–41] (Table 3). The majority of studies focused on unwanted positive symptoms (such as tremor and dyskinesias), rather than hypokinetic symptoms.

3.5 Key Findings

Study findings are summarised in Table 2.

Dyskinesia:

The frequency of unawareness of dyskinesia severity ranged from 19.00%[40] to 66.00%[42]of cognitively intact people with PD. Only one study found participants to over-estimate their dyskinesias[41]. In all other studies participants under-estimated the presence and/or severity of involuntary movements. Under-reporting of dyskinesias correlated with increasing symptom severity[11,37,38], older age[42], executive dysfunction[34,36] and, in one study, left sided predominance of PD symptoms[39].

Bradykinesia:

Two studies by Amanzio et al. did not identify evidence of altered awareness of hypo-bradykinesia when OFF dopaminergic medication, whilst two groups reported by Maier et al. did have reduced awareness for negative motor symptoms, in 54.80%[38] and 53.90%[42] of subjects. Under-reported bradykinesia OFF dopaminergic medication was typically mild, and correlated with reduced perfusion in right inferior frontal gyrus on FDG-PET[38].

General Physical Ability:

When considering general physical ability and ADLs, no evidence of loss of awareness was shown overall[2,43,44]. A discrepancy between patient and informant reports of ADL functioning was seen in the study reported by Leritz et al, but controlling for MMSE rendered this effect non-significant[2]. Fleming et al. found no discrepancy between informant and patient ratings of physical functioning and quality of life[43].

4. Discussion

Altered awareness of motor symptoms in PD is common and has been the subject of a wide range of investigations, often with conflicting findings. The incidence of partial or complete unawareness varies from two thirds of individuals[42] to less than a quarter[39]. Some studies have found under-reporting of symptoms to be commoner in people with milder involuntary movements[11,42], whilst others have demonstrated an association between increasing severity of motor symptoms and the incidence of unawareness[37,38]. These opposing results could indicate that there is bimodal distribution of unawareness, with very mild symptoms going unnoticed early on due to their insidious onset and lack of impact on overall motor functioning, whereas later in the disease course impairments in the neural processes controlling awareness cause under-reporting of more severe symptoms.

An important consideration is the severity of symptoms which go unnoticed. This is inherently difficult to quantify, particularly as different studies use different (sometimes bespoke) rating scales for symptom severity and degree of unawareness. Maier et al. 2015[42] based symptom severity classification on expert physician opinion using the UPDRS-III scales[45]. They found 58.85% of cognitively intact PD participants to be unaware of mild symptoms, 34.46% unaware of moderate symptoms and 4.17% unaware of severe symptoms. Maier et al. 2012[37] found that the majority of participants showed a degree of symptom unawareness, with the unnoticed symptoms most commonly being mild (46.43% of unnoticed symptoms) or moderate (35.71% of unnoticed symptoms), and only 16.07% being severe. A very small proportion of the unnoticed symptoms were very severe (1.79% of all unnoticed symptoms). Amanzio et al. 2010[34] asked physicians to rate unawareness of symptoms, rating this from 0 (good awareness) to 4 (total loss of awareness). Mean physicians scores were 1.36 for dyskinesia unawareness and 0.24 for hypo-bradykinesia unawareness, indicating that unawareness was typically mild, but clearly worse for dyskinesias than hypo-bradykinesias. Maier et al. 2016[38] asked participants and physicians to rate the severity of motor symptoms during 15 tasks, with symptoms being rated out of 4 as per the UPDRS-III (where 0 is no symptoms and 4 is symptoms which prevent the task being performed). The total possible discrepancy score was 60. Overall participants had a discrepancy score of 2.26 OFF medication (range 0-8, SD 2.34), and 3.06 ON (range 0-10, SD 3.10). Therefore, the absolute difference in symptom scoring between people with PD and physicians was relatively small. These findings indicate that unawareness of mild to moderate motor symptoms is common, but only a very small minority are unaware of severe symptoms.

Motor symptoms can be divided into the positive, dyskinetic movements experienced in the ON state, when dopamine levels are highest, and the negative, hypokinetic issues experienced OFF medication, where dopamine levels are low. Amanzio et al. 2010[34] found awareness of bradykinesia in the OFF state to be greater than dyskinesia awareness ON, implying a negative effect of dopamine on awareness. Loss of awareness for dyskinesias was associated with lower scores on the Wisconsin Card Sorting Test, suggesting involvement of the prefrontal cortex. However, it should be noted that subjects reported greater anxiety and depressive symptoms OFF medication, which could have an impact on symptom perception. The same research group[35] subsequently demonstrated a link

between dyskinesia awareness and metacognitive global monitoring, monitoring resolution (processes involved in internally assessing the likelihood of a response being correct) and control sensitivity (the degree of correlation between subjective confidence that a response is correct, and a decision to give that response). This implies that people with PD and reduced awareness may be impaired at monitoring their own performance and using feedback appropriately.

These results are consistent with work using a mirror box task to manipulate participants' perception of their own movements[33]. A hand is placed inside the mirror box, and the participant instructed to move it in a particular direction. Placement of a mirror creates the illusion of movement in the opposite direction, so the direction of the perceived movement is incongruent to that expected. In healthy controls this causes a subjective feeling of strangeness, which is attributed to the mismatch between the planned movement and the visual feedback received. People with PD and reduced awareness of their dyskinesias showed altered experiences during the mirror box task, reporting both congruent and incongruent movements to feel equally strange. This implies that neural mechanisms monitoring planned vs actual movement are malfunctioning, with subsequent difficulties discriminating between accurate and inaccurate execution of planned movements.

Theory of mind (ToM) has also been linked to symptom awareness, further implicating the prefrontal cortex[46]. ToM refers to the ability to understand and describe other people's mental states. It can be divided into cognitive ToM - the understanding of beliefs and intentions; and affective ToM - understanding emotions and feelings. The prefrontal cortex is implicated in both forms of ToM, with cognitive ToM linked to the dorsomedial prefrontal cortex, and affective ToM linked to the ventromedial prefrontal cortex[47]. Palermo et al.[36] observed affective ToM performance to be linked to awareness of motor symptoms, unlike cognitive ToM. Therefore, the ventromedial prefrontal cortex may play a role in awareness of motor symptoms. The same study identified a link between performance on the Trails task and a dyskinesia self-monitoring task, further implicating executive functioning and the prefrontal cortex.

The neural correlates of altered awareness of unwanted motor symptoms were investigated using FDG-PET by Maier et al.[38] When OFF dopaminergic medication, loss of awareness for hypokinesia correlated with decreased perfusion in the right inferior frontal gyrus. In the ON state, altered awareness of positive or negative motor symptoms was linked to greater perfusion of the left inferior frontal gyrus, bilateral medial frontal gyrus, right superior frontal gyrus and right precentral gyrus. When specifically considering dyskinesias in the ON state, unawareness was linked to greater metabolism in the bilateral postcentral mid-cingulate cortex and left paracental lobule. These findings lend weight to the hypothesis that different neural circuits underpin awareness of hypokinesia and dyskinesia, and that dopamine replacement directly impacts on motor self-awareness.

PD and DLB are often defined as a purely dopaminergic disorder, but performance of a number of other neurotransmitters are also altered, and may play a role in altered symptom awareness. Acetylcholine is heavily implicated in the process of constructing conscious experience, in particular the basal forebrain and rostral brainstem cholinergic pathways[31]. Antagonistic agents can induce hallucinations and altered consciousness, whilst in AD and DLB the use of cholinesterase inhibitors

may alleviate psychotic symptoms. Cholinergic activity is significantly reduced in PD, with profound deficits found in PDD and DLB, to a greater extent than those found in AD[48,49]. Clearly acetylcholine deficits are therefore not the sole reason for loss of symptom awareness, as awareness is typically more severely affected in AD than in PD[50].

In healthy adults, manipulation of dopamine has a mixed effect on awareness. L-dopa has been found to improve awareness of memory retrieval performance[3], an effect which could be mediated by dopamine stimulating GABAergic activity in the medial PFC, ACC and right insula[23]. Clos et al. found potentiation of dopamine release using low dose haloperidol reduced meta-memory when detecting new items, but improved meta-memory for previously presented items[4]. In a perceptual task, blockage of the D2 and D3 receptors with amisulpiride had no impact on confidence[30]. These mixed results may reflect different neural mechanisms underpinning awareness of performance in different cognitive domains, or the varying impacts of different pharmaceutical agents on the neurotransmitter and receptor brain milieu. Three major dopaminergic systems are implicated in altered awareness in PD: the nigrostriatal circuit; the mesolimbic circuit; and the mesocortical circuit. PD is characterised by a progressive dopaminergic deficit in the nigrostriatal circuit, which is treated by dopaminergic medications. In doing so it is possible that dopaminergic overload occurs in the mesolimbic and mesocortical circuits, and this has been hypothesised to be a cause of loss of symptom awareness[11].

Noradrenergic neurons in the locus coeruleus are severely affected in PD, and this potentially contributes to motor and non-motor symptoms. The locus coeruleus receives glutaminergic afferents from the OFC and ACC, areas known to be involved in self-awareness. In healthy controls, the inhibition of central noradrenergic transmission can improve metacognition, via better recognition of inaccurate choices[30]. However the specific role of noradrenaline in symptom awareness in PD has not been investigated. The serotonergic system is also compromised in PD, and implicated in the development of hallucinations and other psychotic symptoms[51], but the potential consequences for symptom awareness are unknown.

It is possible that cognitive performance modulates awareness of motor symptoms, i.e. individuals with more severe cognitive impairments also showing greater difficulties with awareness[32,33]. Leritz et al.[2] found differences in MMSE to explain discrepancies in self and carer ratings of ADL ability, and Maier et al. 2015[42] found increasing age to correlate with worsening symptom awareness. Seltzer et al.[32] identified worsening cognition as a correlated to greater symptom unawareness. Contrary to this hypothesis, Palermo et al.[36] found no association between global cognition and dyskinesia awareness. Most studies have focused on cognitively intact individuals, and there is a need for high quality research studies to elucidate the impact of cognitive functioning on motor symptom awareness. There is also a lack of studies of motor symptom awareness in DLB.

Classical descriptions of loss of symptom awareness come from the stroke literature, and it is well recognised that individuals with damage to the right hemisphere are particularly affected. Extrapolating from this, it is logical to hypothesise that people with PD affecting the right

hemisphere in particular (and consequently displaying left sided motor symptoms at onset) might experience more severe loss of symptom awareness. Some studies support this hypothesis[37–39], although others have found no association[35]. The issue is further clouded by a trend for right sided symptoms to cause greater functional impairments, most likely due to the predominance of right handed individuals[2].

There are a number of methodological limitations to the current literature in PD. Most studies have focussed on seemingly cognitively intact individuals, as defined by a tool such as the MMSE. The MMSE is a useful screening tool, but is insufficient to accurately distinguish normal cognition from MCI or early dementia in PD. The Movement Disorders Society has developed detailed testing recommendations for the diagnosis of MCI due to PD, and future studies would benefit from using these more robust criteria[52,53]. There is a paucity of studies specifically investigating the impact of cognitive decline on symptom awareness, and very few studies to date have assessed changes to awareness longitudinally. Given the chronic nature of PD and high incidence of progressive cognitive decline, longitudinal studies are needed to accurately establish the neural underpinnings of symptom awareness, the most effective assessment techniques and ultimately generate novel tools to support those affected.

Many studies have relied on discrepancy scores as a measure of awareness. These are potentially open to significant bias if the informant is unduly influenced by a desire to protect the participant and therefore under-report symptoms, or is experiencing significant carer burden and consequently over-report symptoms. Furthermore, even a close relative may not be fully aware of an individual's exact mental state or experience of living with subtle cognitive change.

Altered symptom awareness in neurodegenerative conditions can greatly exacerbate the impact of the primary condition itself. Those affected may not seek appropriate help and support or refuse essential care. Studies of people with Alzheimer's disease have reported worsening insight to be associated with greater carer burden and strain. As the world's population ages the prevalence of Parkinson's is predicted to increased significantly[18]. Understanding how symptom awareness changes during the life course of PD, and the impact this has on those affected and their significant others and caregivers is a vital step in the pathway towards developing effective management and therapeutic techniques.

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Table 1. Studies of altered awareness of motor symptoms in PD and DLB.

AUTHORS	STUDY GROUPS	AGE (Years†)	DISEASE DURATION (Months†)	COGNITIVE STATUS (MMSE unless otherwise stated†)
Amanzio 2010 [34]	25 people with PD & motor fluctuations (13♀12♂)	59.12 (range 39.00-74.00)	137.60 (range 84.00-240.00)	27.80. Excluded if MMSE <24.00
Amanzio 2014 [35]	48 people with PD & motor fluctuations (22♀26♂)	65.79 (6.52)	137.76 (78.24)	27.65. Excluded if MMSE <24.00
Fleming 2005 [43]	64 people with PD (sex ratio not stated)	74.41 (5.72)	Not stated	MMSE not stated. Those with dementia excluded
Jenkinson 2009 [33]	6 people with PD & anosognosia (2♀4♂) 11 with PD & intact awareness (6♀5♂) 22 controls (12♀10♂)	Anosognosia 69.67 (8.76) Intact awareness 65.20 (7.63) Controls 66.86 (6.82)	Not stated	PD & anosognosia 26.67 (2.80) PD & intact awareness 29.23 (1.12) Controls 29.23 (0.81)
Leritz 2004 [2]	32 people with Left sided PD (13♀19♂) 16 people with Right sided PD (7♀9♂)	Left 64.05 (7.14) Right 62.38 (7.36)	Left mean 14.13 years (7.84) Right 13.00 (3.88)	Left 28.00 (1.90) Right 29.06 (1.12) Excluded if MMSE<=24.00
Maier 2015 [42]	104 PD patients (36♀68♂)	Median 66.50 (range 41.00-80.00)	Median 72.00 (range 0-240.00)	Median MMSE 29.00 (range 27.00-30.00) Excluded if MMSE<27.00
Maier 2012 [37]	28 people with PD (8♀20♂)	60.32 (9.68)	Mean 7.68 years (9.68)	28.71 (1.41) Excluded if MMSE <=25
Maier 2016 [38]	31 people with PD (8♀23♂)	65.13 (6.51)	104.04 (54.84)	28.74 (1.18)

Martinez-Martin 2003 [44]	60 people with PD (34♀26♂)	66.61 (7.97)	Not stated	MMSE not stated (5 subjects had mild to moderate cognitive impairment)
Palermo 2017 [36]	41 PD & motor fluctuations (18♀23♂)	65.00 (6.58)	Median 132.00 (IQR 108.00-168.00)	28.32 (1.37)
Pietracupa 2013 [39]	30 PD & levodopa induced dyskinesias (17♀13♂) 15 controls (8♀7♂)	PD group 67.40 (8.20) Controls 66.80 (9.90)	138.00 (64.80)	28.10 (2.10) Excluded if MMSE <=26.00 (MMSE for control group not stated)
Pillai[54]	30 PD-MCI (8♀22♂) 17 non-amnestic MCI (6♀11♂) 33 amnestic MCI (16♀17♂)	PD-MCI 67.80 (7.40) Non-amnestic MCI 69.80 (5.90) Amnestic MCI 69.6 (6.10)	Not stated	Mean (SD) MoCA: PD-MCI 23.70 (0.30) Non-amnestic MCI 23.00 (2.90) Amnestic MCI 20.60 (2.70)
Seltzer 2001[32]	32 PD (12♀20♂) 31 AD (17♀14♂)	PD 72.20 (11.40) AD 76.60 (8.00)	PD 64.80 (44.40) AD 32.40 (19.20)	PD 23.40 (11.40) AD 18.50 (5.20)
Sitek 2011a [40]	21 with PD & dyskinesia (11♀10♂)	63.29 (8.82)	146.28 (56.76)	27.53 (1.86). Excluded if MMSE <25
Sitek 2011b [41]	25 people with PD & dyskinesias (13♀12♂) 21 PD no dyskinesia (6♀15♂) 23 with Huntington's disease (9♀14♂) 20 cervical dystonia (12♀8♂)	PD & dyskinesia 65.68 (10.03) PD no dyskinesia 64.67 (7.59) HD 49.83 (11.12) Cervical dystonia 51.75 (12.98)	PD & dyskinesia 144.00 (SD not given) PD no dyskinesia 48.00 (SD not given)	PD & dyskinesias 27.00 (mean, SD not given) PD no dykinesias 28.00 (mean, SD not given) HD 26.00 (median) Cervical dystonia 28.50 (mean, SD not given)
Vitale 2001 [11] ‡	13 people with PD & dyskinesias 9 people with HD (sex ratio not given)	PD group median 60.10 (range 49.00-77.00) HD group median 58.50 (range 31.00-71.00	PD group median 138.00 (range 72.00-240.00)	All MMSE=>23; mean MMSE not stated.

† Age, disease duration and MMSE values are given as mean and standard deviation unless otherwise stated.

‡ All studies reporting the source of participants recruited from specialist hospital clinics; Vitale et al. did not state the recruitment source.

Table 2. Awareness Assessment Methodology & Key Findings

AUTHORS	MOTOR ASSESSMENT METHODS & KEY FINDINGS
Amanzio 2010 [34]	GAM: physician observation of subject awareness of hypo-bradykinesia & dyskinesia (scale range 0: good awareness to 4: no awareness of motor symptoms). Mean GAM of 1.36 for dyskinesias ON & 0.24 for hypo-bradykinesias OFF medication Discrepancy scores based on self-assessment & examiner assessment of hypo-bradykinesias & dyskinesias during simple motor tasks. Dyskinesias rated from 0 (none) to 3 (severe); on average subjects rated dyskinesias as 0.71 less severe than examiners did. Reduced dyskinesia awareness ON medication (which correlated with executive function). Preserved awareness of hypo-bradykinesia OFF
Amanzio 2014 [35]	GAM; discrepancy scores for hypo-bradykinesia & dyskinesias (as per Amanzio 2010). Absolute values for these not reported. Reduced awareness of dyskinesias associated with metacognitive global monitoring, monitoring resolution & control sensitivity. No associations with disease duration, symptom laterality, age or L-dopa dose. Participants had intact awareness of hypo-bradykinesia.
Fleming 2005 [43]	Questionnaires (CES-D & PDQ-39) completed by subjects & informants & discrepancies between scores calculated. There was no significant differences in ratings of disability, QoL and physical activity.
Jenkinson 2009 [33]	Subjects rated how 'strange' movements felt during a mirror box task (range 0 'no sense of strangeness to 9 'very strange'). Anosognosic group rated congruent movements as feeling strange (mean 3.83) unlike those with intact awareness (0.68) & controls (0.27). No difference in ratings on incongruent movements (anosognosic group 4.24, intact awareness group 2.86, controls 3.64). Anosognosic PD group unable to distinguish congruent & incongruent movements, suggesting failure to differentiate between intended and actual movements.
Leritz 2004 [2]	Patients & carers completed motor & ADL parts of UPDRS, plus Schwab & England ADL scale (where 100%: complete independence, 1%: total dependency). Patients self-rated as less impaired on ADLs compared to carers (Schwab & England 53.50% vs 46.33 in left sided group, 60.00 vs 53.33 in left sided group) but controlling for MMSE rendered this non-significant. Symptom laterality did not affect awareness.
Maier 2015 [42]	Discrepancy scores calculated from subject & expert ratings of positive & negative motor symptoms during filmed motor tasks. 66.35% had impaired awareness of motor symptoms. 58.85% were unaware of mild symptoms, 36.46% unaware of moderate symptoms, 4.17% unaware of severe symptoms & 0.52% unaware of very severe symptoms. Older age correlated with greater unawareness. 7.80% of subjects reported a symptom not noticed by expert raters.
Maier 2012 [37]	Discrepancy scores calculated from subject & expert ratings of positive & negative motor symptoms during filmed motor tasks (UPDRS-III scales). 60.71% had impaired awareness. Regarding unnoticed symptoms, 46.43% were mild, 35.71% moderate, 16.07% severe & 1.79% very severe. Motor symptoms & specifically left sided symptom severity OFF were associated with unawareness. Gait instability correlated with unawareness.

Maier 2016 [38]	Discrepancy scores calculated from subject & expert ratings of positive & negative motor symptoms during filmed motor tasks (as per Maier 2015[42]). Total severity scores for motor symptom unawareness calculated based on 15 possible symptoms, each rated from 0 (symptom absent) to 4 (unable to perform action but unaware of this). Total possible score 60. Mean total unawareness scores of 2.26 ON & 3.06 OFF. OFF medication: hypokinesia unawareness linked to reduced perfusion in right inferior frontal gyrus and left sided PD onset. ON medication: overall unawareness of hypokinesia and dyskinesia correlated with greater metabolism in prefrontal regions and right precentral gyrus
Martinez-Martin 2003 [44]	Patients, carers & physicians rated symptoms on a modified UPDRS-ADL. Ratings of physical disability by patients were marginally higher, but the only significant difference between raters was on the 'falling' item (where patients & carers rated this as worse than physicians). Depression weakly influenced self-rating of disability & ADL scores. Carer burden did not influence inter-rater group agreement.
Palermo 2017 [36]	Dyskinesia awareness rated by physician using the GAM, & the Dyskinesias-Subtracted Index (the difference between subject & physician rating of dyskinesias during set motor tasks, with possible scores from 0: dyskinesia absent to 3: severe dyskinesia). Mean GAM score 1.51 (SD 1.00), mean Dyskinesias-Subtracted Index 1.27 (SD 0.81) Dyskinesia unawareness was associated with the Reading Mind in the Eyes & Trail making tasks performance, but not with global measures of cognition.
Pietracupa 2013 [39]	Patients self-rated their dyskinesias in 7 body areas during actions & on watching film of these, rating severity from 0 to 4. Discrepancy scores calculated comparing patient ratings with physician ratings. Patients' mean rating 5.50 (SD 4.30) vs physicians 7.60 (SD 4.20) 23.3% were completely unaware of dyskinesias during actions but 93.70% recognised dyskinesias on watching a film of themselves. Awareness was worse for truncal dyskinesia compared to limb. Unawareness greater in those with left sided symptoms predominance.
Pillai[54]	Discrepancy scores between patient and informant on the Anosognosia-Questionnaire Dementia (30 ADL questions scored from 0 to 3). PD-MCI subjects self-rated as being more impaired than informants (mean discrepancy -4.60, SD 12.30). Amnestic & non-amnestic MCI groups self-rated as being less impaired (mean discrepancy scores of 1.40 & 1.60). 11.40% of those with PD-MCI showed anosognosia for ADL ability (defined as a discrepancy score of >=14); rates in the other groups were similar. In PD-MCI depressive symptoms were associated with lower self-appraisal scores.
Seltzer[32]	Discrepancy scores (patients vs carers) using Patient Competency Rating Scale, Motor-Unified Rating Scale for Parkinsonism & Clinical Dementia Rating Scale. Clinician ratings on the M-URSP. Patients rated themselves as less impaired on the M-URSP compared to carers. Carer motor scoring correlated with clinician ratings, suggesting this is a valid measure. Reduced awareness correlated with impaired cognition (particularly memory) in the PD group.
Sitek 2011a [40]	Patients & study partners rated motor symptoms on pre-recorded films, and rated symptoms experienced by the patient (max scores 15 for parkinsonian symptoms, 15 for dyskinesias). No overall significant differences between patient & partner ratings. Raw data showed 9% of patients to be unaware of all dyskinesias, and 19% significantly under-estimated dyskinesias (defined as more than 4 point discrepancy).

Sitek 2011b [41]	Patients & informants completed the Motor Impairment Scale (rating patient motor symptoms in comparison to reference films) & the Self-Assessment Parkinson's Disease Disability Scale for ADLs. People with PD and dyskinesias over-rated choreic movements.
Vitale 2001 [11] ‡	Patients evaluated their dyskinesias during specified motor tasks. Physicians rated dyskinesias on the Abnormal Involuntary Movement Scale & the Goetz Dyskinesia Rating Scale. Physicians rated unawareness from 0 (fully aware) to 8 (totally unaware). Significant negative relationship found between total score on AIMS & unawareness of movements on standing, & between upper limb AIMS score & unawareness at hand pronation. Unawareness did not correlate with total UPDRS, Goetz score or disease duration.

Abbreviations: ADL Activities of Daily Living; AIMS Abnormal Involuntary Movement Scale; CES-D Centre for Epidemiological Study-Depression; GAM Global Awareness of Movement; PDQ-39 Parkinson's Disease Questionnaire; UPDRS Unified Parkinson's Disease Rating Scale

Table 3. Study quality summary.

AUTHORS	STUDY CHARACTERISTICS
Amanzio et al. [34]	Cross-sectional study. Well characterised group. Assessed ON and OFF medication.
Amanzio et al. [35]	Cross-sectional study, good group size. Well characterised group. Group assessed ON and OFF medication.
Fleming et al. [43]	Cross sectional study, good group size but limited neuropsychological characterisation. Medication status of PD participants during assessment not given.
Jenkinson et al. [33]	Case-control study. Small group sizes but well characterised. Medication status of participants during assessment not given.
Leritz et al. [2]	Cross-sectional study. Good group size, well characterised. All participants tested ON medication.
Maier et al. [42]	Cross-sectional study. Good group size, well characterised. All participants tested ON medication.
Maier [37]	Cross-sectional study. Moderate group size; well characterised. Participants assessed ON and OFF medication.
Maier [38]	Cross-sectional study. Moderate group size. Assessed ON and OFF medication.
Martínez-Martín[44]	Case-control study. Good group sizes; limited cognitive characterisation. Medication status during assessment not stated.
Palermo[36]	Cross-sectional study. Moderate group size; well characterised. Participants assessed ON and OFF medication.
Pietracupa [39]	Cross-sectional study. Moderate group size; well characterised. All participants assessed ON medication.
Pillai[54]	Cross-sectional study. Moderate group sizes; well characterised. Medication status during assessment not stated.

Seltzer[32]	Cross-sectional study. Moderate groups sizes; well characterised. Medication status during assessment not stated.
Sitek [40]	Cross-sectional study. Small group sizes; well characterised. Assessed ON medication.
Sitek [41]	Case-control study. Small group sizes; well characterised. PD participants assessed ON medication.
Vitale [11]	Case-control study. Small group sizes; limited group characteristics reported. Excluded if MMSE <23. Medication status of PD participants during assessment not given.