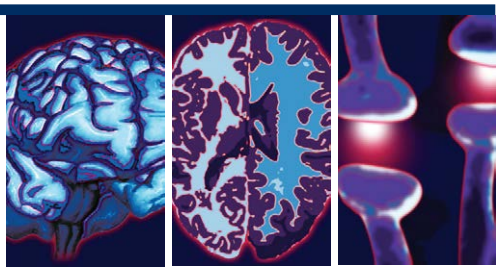
Review



Cognitive and Psychological Anomalies in Parkinson's Disease: An Insight into Non-Motor Characteristic Features

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Abstract

While most of the clinical concerns for Parkinson's disease (PD) are limited to the cardinal motor abnormalities, non-motor features like cognitive and psychological anomalies are also acquired ample of importance in last few decades. Progressive research has showcased several obvious incidences of cognitive and psychological anomalies in the pathophysiology of PD. It has been reported that, almost 30% PD sufferers show different degree of cognitive impairment but lack of awareness or negligence makes it difficult to diagnose it, at the initial stage of the disease. As a result, cognitive and psychological impairments continue to increases progressively and deteriorate the quality of life of the patient. It is presumable that, early detection of PD can be achieved by the identification of specific set of cognitive and psychological anomalies and the similar scope might open up new avenue in the non-invasive diagnosis of PD. In the present review, we have accumulated all the timely documentation on cognitive and psychological anomalies in PD and highlighted most of the non-motor features with rational justification for the relevance of their study in the early diagnosis of PD.

Keywords:

Parkinson's disease, Cognition, Psychology, Depression, Anxiety, Memory

Introduction

Parkinson's disease (PD) is a chronic, insidious neurodegenerative disorder characterized by classical symptoms like bradykinesia, rest tremor, rigidity, and postural disturbances [1]. The pathophysiological scenario of PD includes the cytotoxic aggregation of α-synuclein, which forms Lewy Body-the eosinophilic hollow structure, regarded as the 'hall-mark' feature for PD [2,3]. Besides motor abnormalities [4], PD also has been reported with few non-motor psychological [5] and cognitive anomalies [6], which are comparatively less highlighted in last ten decades, since PD discovery [7]. During clinical diagnosis by Aarsland *et al.* 19% cognitive deficit PD patient were identified, which is one of the notable findings exploring the association between PD and cognitive impairment [8]. Progressive research has showed that, cognitive impairment with or without dementia is also a predominant feature of PD [9]. Statistically, PD with dementia is having a global prevalence rate of 30%, which is evident in a cross-sectional study by Aarsland *et al.* and they also have suggested almost 80% life-long risk are there with similar types of patients [10].

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It has been reported that, PD patients often face it troublesome to concentrate in deep thinking and feel distracted or disorganized in planning specific tasks [11,12]. Moreover, attention deficiencies are also common in PD patients when they were accessed for group discussion or conversation. Most of the time 'missing information' or 'weak memory' feeling appears among the sufferers of PD [13]. Another notable fact regarding memory impairments reflects among PD patients, while they try to express their feeling in verbal way. Lack of proper word selection, incomplete sentence throwing and stumbling during conversation is quite common in PD [14]. Anger and anxiety are also evident among PD patients while managing common household affairs, which frequently interfere in the quality of life of the sufferers [15]. Studies have shown that, stress and depression also quite common in PD [16] and sometimes adverse effect of prescribed medication deteriorates the scenario even worse [17,18]. Though, cognitive impairment and dementia both affect memory function but, cognitive impairment is considered as the far early stage of dementia and reports have shown that, most of the cases cognitive impairment develops dementia in the late stages of PD [19,20]. Majority of therapeutic interventions for Parkinsonian dementia are still under investigation and available drug Rivastigmine tartrate (Exelon®) has been marketed with three adverse side effects like gastrointestinal adverse reactions, Allergic dermatitis and increased cholinergic activity [21].

Sometimes, researchers represent psychological and cognitive anomalies in PD as mild cognitive impairment and motor disabilities become predominant concerns to physicians [22]. Hence, the severity and apprehensions related to non-motor symptoms gets lesser importance [23]. Though, proper scientific studies and justified application of such non-invasive cognitive and psychological tests could open up new possibilities to innovate early diagnostic tools for PD. Here in this present study, we have accumulated all the relevant information on cognitive impairment and psychological anomalies and highlighted the importance of such alterations in early diagnosis of PD (Figure 1).

Cognitive Impairments in Parkinson's Disease

By definition, cognition is the conglomeration of several different mental skills and activities, which precipitates in the behavior and intelligence of an individual [24]. In mechanistic way, cognition is described as the synchronized processes of brain function that helps an individual to discover the ambient environment around itself and also assists to interact in a controlled and appropriate

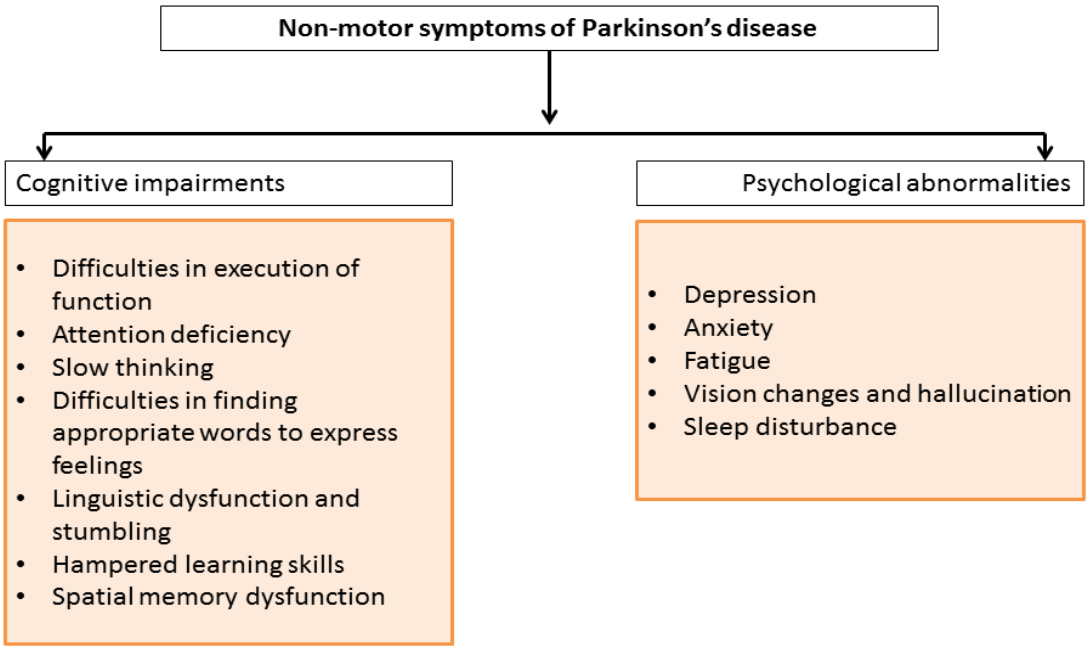

Figure 1: Non-motor symptoms of PD and their types.

manner [25]. Proper cognitive assistance explores the sense of perceptions, stores it in memory and retrieves the same depending upon need and/or usage [26]. This is the generalized path to boost and enrich the memory ability, which reflects in the process of learning, planning, solving, thinking, and linguistic skill development [24,27].

Abnormalities in neuronal structure and function are highly responsible for dysregulation of said cognitive processes, which are evident in PD [28]. PD is well-known as a movement disorder clinically characterized by resting tremor, bradykinesia, postural instabilities [1,7]. However, recent progress of research and studies have highlighted the co-occurrence of non-motor abnormalities in PD [5,29] and thereby, raising the concern to consider the cognitive impairments and psychological anomalies as an important feature for PD pathology [23,29]. In last decades, several experimental evidences have linked the occurrence of cognitive impairment with PD. In an earlier report, application of 'Society Task Force guidelines' on diagnostic criteria for the evaluation of mild cognitive anomalies in PD has been highlighted, which represents a novel approach justifying the relevance of such tool in PD [11,12]. Cooper *et al.* have reported the scenario of cognitive impairment on the untreated PD patient and found a significant correlation exists in between cognitive disabilities and motor impairments [30]. Exclusive works by Janvin *et al.* have represented the types and sub-types of cognitive impairments in PD patients, which further linked the cognitive impairment with the occurrence of dementia [31]. Neuropsychological and clinical heterogeneity of cognitive impairment in PD patient has also been documented with possible links supporting the disease progression towards severe dementia [32].

Movement Disorder Society's special task force is the most appreciated approach in the said field of study, which has reviewed all the possible aspects of cognitive dysfunction in PD [12]. In a large scale clinical study with 873 idiopathic PD patients, Riedel *et al.* have reported that, cognitive impairment is a common incident in PD and having significance in the early diagnosis of the disease [33]. In a multicenter pooled analysis, Aarsland *et al.* have documented the occurrence of mild cognitive impairment in PD patient [34]. In 'The Norwegian ParkWest Study' by Aarsland *et al.* has found similar result in drug naïve PD patients [8]. Another 'prospective longitudinal study' has presented depression, cognitive decline, and physical impairments in patients with PD. The same article is also suggested a possible link relating the events in disease progress [35]. Several cognitive function assessment tools have been introduced in recent years. The Montreal cognitive assessment screening tool is one of the similar kinds, which were employed in the diagnosis of cognitive status of PD patient by several authors in recent years [36]. However, molecular pathological alterations are also linked with the incidence of cognitive deficiency in PD. Mattila *et al.* has documented a study, where α-synuclein aggregation and Lewy body formations were reported to be highly correlated with cognitive impairment in PD [37].

In an earlier report by Perry *et al.* documented the similar correlation with cholinergic system [38]. Beyer *et al.* have studied voxel-based morphometry in magnetic resonance imaging on PD patient and found cognitive impairment is linked with the progress of the disease [39]. However, herbal, dopaminergic medication and certain task test have found to be beneficial for cognitive impaired PD, as it showed improvement among sufferers [40]. Particularly, Hippocampal and prefrontal atrophy has been reported responsible for the cognitive impairment in PD [41]. Another study has claimed the possibility of cognitive impairment in Parkinson's disease could be due to non-dopaminergic lesions [42]. Pharmacological studies on cognitive improvement in PD have showed promising outcome in recent years [35]. Though, applications of most of the drugs are still debated. However, the efficacies of the drugs like Donepezil, Atomoxetine, and Citicoline cannot be ruled out owing to their promises [43]. Earlier it was believed that, the occurrence of cognitive impairment in PD is limited to mid-to-late stage of the disease progress but, recent progress of research have showed that, mild cognitive changes is quite common in early stages of PD and hence, opening an avenue of research scope for early diagnosis of the disease. Majority of cognitive impaired PD in late stage develop dementia but, early-to-middle stage of the disease is predominantly cognitive impairment, which accounts ½ to ¼th of the total PD population [19].

Types of Cognitive Impairments

Cognitive impairments in PD are of several types, which are mainly focused on particular

functional disabilities. It is reported that, the severity of the cognitive impairment varies with the duration of the disease or even person to person. The functional anomalies related to behavior or intelligence is highly governed by the implication of cognitive attributes in human [44]. The major cognitive differences a physician trace in the early stage of PD includes abnormalities in execution of functions, attention difficulties, slow thinking, trouble in word selection, difficulties in remembering information, learning, hampered spatial learning and imaging capability [45,46].

■ Difficulties in execution of function

These are the initial feelings of cognitive impairment to an individual suffering from early stage of PD [45,47]. In many instances, people often ignore the fact thinking it a transient effect of work pressure and stress. However, chronic ignorance deteriorates the situation even worse and several signs of cognitive disabilities start to express. Lack of abilities in making plans, goal formulation, process evaluation are the basic feature of function execution related cognitive abnormalities [45,48]. In the study by Koerts *et al.* difficulties in execution of function has been evaluated through 'Cognitive Effort Test' and explored the vulnerability of the PD patient in performing daily-life works [49].

■ Attention deficiency

It is also known as attention deficit hyperactivity disorder (ADHD) which is another cognitive disability observed in PD [50]. Though, the actual relationship is still speculative but both the diseases act on same platform i.e., substantia nigra [51]. Generally, the symptoms of ADHD start at childhood ages of the sufferer and proceeds into adulthood [52]. Most of the cases attention deficiency has been observed in PD but, it is tough to evaluate whether the same patient had ADHD in childhood or not. Hence, the conclusive association is equivocal, except one report by Walitza *et al.* where 'Wender Utah Rating Scale' was used to monitor the ADHD score and it was found that, PD patients were suffering from increased attention deficit, hyperactivity and anxious and depressive behavior [50].

■ Slow thinking

It is another feature in cognitive impaired PD patient. Comparatively such PD patients take longer time and efforts to complete tasks than a common people [14,53]. Reports have showed that, such slow process of thinking is associated with the injury or impairment in Fronto-striatal region of brain [54,55]. PD patients also find it difficult to find appropriate word to express the feelings [56]. Though, similar problems have been reported with many other diseases also [57]. Separate study, Merims and groups, Freedman and groups have reviewed the occurrence of such word-finding problem [58,59]. The same study also emphasized this phenomenon, as an inseparable part of PD, if mild motor abnormalities are present in the patients [60].

■ Linguistic dysfunction

Another study highlighted the genetic background underlying linguistic dysfunction and explored that, lack of function or absence of apolipoprotein E epsilon4 allele is responsible for such behavior [61]. Language impairment in PD, also eloquently discussed in the work of Bastiaanse and Leenders, where detail about nature, dissociation, and progression of linguistic impairment in terms of syntactic, action-verb, and action semantic skill have been discussed [14]. Moreover, in a meta-analysis Henry *et al.* have showed that, verbal fluency significantly deteriorates in PD patients while compared with matched control [62]. Trouble in learning new things or remembering the information is also quite common in cognitive deficit PD patient [63].

■ Hampered learning skill

Molecular mechanism of hampered learning skill is associated with dopamine depletion. It has been reported that, dopamine depletion in striatal region reduces the functional symmetry dorsolateral prefrontal circuit, which is extended towards orbito-frontal pathway-the region responsible for reward-based learning in human [40,64].

■ Spatial memory functions

Cognitive deficient PD patients are reportedly lacking the ability to image the previously executed tasks and spatial memory functions [65,66]. Possin *et al.* executed a study for spatial memory function and found that, PD patients are having significantly lower ability to memorize or image spatial locations or shapes than randomly selected control people [67]. In another study, Pillon *et al.* found that lack of spatial recognition is linked with dopamine depletion and suggested striatofrontal dysfunction could be the crucial player in such cognitive impairment [68]. In a recent report,

the very same dopamine involvement has been highlighted with special reference to modulation in hippocampal-striatal functions in PD [66]. Together, most of the cognitive impairments in PD are directly or indirectly influenced by dopaminergic homeostasis and such rationale justifiably put forwards the association between cognitive impairment and PD.

Psychological Abnormalities in Parkinson's Disease

The report by Celesia and Wanamaker is one of the pioneer works focused on psychological aspects of PD [69]. In that particular report, the authors have documented the first ever clinical evidence of psychiatric abnormalities among 153 PD patients, majority of which were affected with variable degree of psychosis [69]. With the special emphasis on the non-motor characteristics of PD, the study also flagged up the well-known cross-talk between cognitive impairment and dementia [70]. Growing interests and studies on neuropsychiatric background of PD have unveiled several hitherto unexplored facts and such endeavors reflected in the progresses made so far in the therapeutics of PD [71]. McKeith and Cummings highlighted the behavioral as well as the psychological perspectives of PD [70] while, patterns of psychological problems in PD have been discussed by Macht *et al.* [72]. Both articles have emphasized the co-incidence of psychological events as crucial characteristic features in the pathobiology of PD.

Similar notion was also evident from the studies by MacCarthy *et al.* where 136 PD patients were accessed for 'Self-report measures' and result was significantly positive for the statement of co-occurrence of motor and psychological abnormalities among the patients [73]. However, early and late onset of PD with psychological anomalies was a topic of debate since the origin of the concept. The study by Schrag *et al.* intercepted the fact in a questionnaire base study with 141 PD patients (75 early-onset, 66 late-onset) and found that, psychosocial factors play important role in the quality of life in young patients with PD [74]. Furthermore, study by Janvin *et al.* also highlighted the similar involvement of psychological abnormalities in PD patients and provided a timely note on the influences of dementia in PD pathology [75].

Types of Psychological Abnormalities

■ Depression

Among several psychological abnormalities in PD, incidence of depression is most prevalent. Van Praag *et al.* reported the association between dopamine depletion and occurrence of psychological anomalies in PD, which was the first ever report of such kind [76]. Later on, Taylor *et al.* re-evaluated the interlinking relationships between depression and the occurrence of PD [77]. In the very next year, Rogers and colleague reported the same phenomena and provided a rational discussion on psychological anomalies in PD and other depressive illness [78]. Together, reports were in line with the crucial involvement of depression in the pathology of PD. However, actual scenario of PD pathology, in respect to depressive behavior, was lacking more justifiable evidences, and it is until the clinical study by Brown *et al.* that made it eloquent [79]. The study was based on a follow-up of 132 cases, and outcome of the study presented a resourceful discussion on depression and disabilities in PD. In another study, the very similar notion of depressive behavior in PD was presented by comparing the equivalent disabilities in control subjects [80].

In the succeeding decades, several research and studies were performed on depressive issues in PD. Among plenty of resources, review sum-up by Dakof and Mendelsohn, Cummings, Brown *et al.* and Lieberman are noteworthy [81-84]. However, discussion on quality of life of PD patients with depression by Schrag is another piece of appreciable work [85]. Torbey *et al.* reviewed the 'Depression rating scales in Parkinson's disease', which is having timely importance in PD research [86]. It has been reported that, variable degree of depression is quite common in PD. According to physicians, depression can occur without any Parkinsonian symptoms in pre-early stage of PD or even it can appear with certain intervals [87]. Neurochemical dysregulation mainly in nigro-striatal region has been postulated as the prime factor underlying long lasting depression in PD [88]. Modulation of dopamine, norepinephrine and serotonin production has been shown promising improvement in the depression oriented chronic illness and in PD also [89]. Some reports also have indicated the potential role of depression in the deterioration of the PD pathology [90]. Very common appearances of PD depression include long lasting sadness, lack of interest, unnecessary

guilty feeling, less attention for self-care, loss of motivation, worry and self-criticism [84].

However, the incident of depression becomes complex and critical when mild symptoms of other closely related disease like dystonia and essential tremors are common with the patient [91]. Similar issue has been discussed by Miller et al and the authors have presented a meaningful discussion resourceful for healthcare professionals in PD [92]. Commonly prescribed antidepressants have been found effective for the PD patients and alongside the medication, exercise, yoga and meditation are advised for better outcome [93,94].

■ Anxiety

Alterations in the neurochemicals are the reported and most valid cause underlying anxiety, which is also quite common in PD [95]. Anxiety or restlessness is defined as the random activity of any animal without particular goal [96]. Among several reports on PD with anxiety, the study by Stein *et al.* is notable and first of similar kind, where the authors studied 24 PD patients with DSM-III-R axis I syndromes and found that, anxiety was evident among 38% of the sufferers [96]. Another study by Dissanayaka *et al.* studied on 79 PD patients and evaluated the presence of anxiety using DSM-IV criteria [95]. The outcome of the study revealed that 25% of the PD patients were suffering from anxiety of different varieties like Panic disorder, generalized anxiety disorder and social phobia [95]. Possible relationship between anxiety and PD is a debated as well as intriguing fact, which was reviewed and discussed by Richard and colleague in several articles and book [97,98]. Together, available information are in line with the assertive notion on the coincidence of the occurrence of anxiety in PD patient.

■ Fatigue

Fatigue is another psychological anomaly in PD, affecting about half of the PD sufferers worldwide [99]. Mild to severe fatigue is evident since the early stages of PD and it can persist till the disease progress [99,100]. There are many overlapping phenology of fatigue with depression and creates a great deal of confusion in particular incidence diagnosis [101]. Moreover, additional symptoms like stress and depression can make the situation even worse [101,102]. There are no conclusive mechanisms have been stated behind the occurrence of fatigue in PD. However, it is assumed that, motor abnormalities like tremor and stiffness might be the crucial factors for muscle tiredness, which is the initial cause of fatigue [103]. It has been reported that, PD patients with fatigue fights a lot for sleep but unable to do so despite severe tiredness [104]. On the other hand, lack of concentration is also found to be associated with mental fatigue [105].

Exclusive works by Van Hilten *et al.* and Friedman *et al.* have highlighted the incident of fatigue in PD patient [106,107]. Similar findings were also reported by Karlsen *et al.* and Abe *et al.* [108,109]. However, intriguing association between physical fatigue and mental fatigue was documented in 2001 by Lou *et al.* [105]. In a study of nine years follow up investigation, Friedman *et al.* have presented the scenario of fatigue in PD patients [107]. Other crucial works by Friedman and colleague have unveiled several aspects of fatigue in PD [104,107]. Documentation on the impact of fatigue on quality of life in patients with PD is available from the study by Havlikova and colleagues [110]. In a summary, fatigue plays an important role in the psychological events in PD and holds crucial determining role in the quality of life in PD patients. Despite several therapeutic hypotheses and approaches, the conclusive cure from fatigue in PD is still remained an unachieved goal. Management of secondary psychological symptoms like sleep disturbance and depression is assuming to be the only option to tackle the fatigue issue in PD, as it is closely tangling with such symptoms [111].

■ Vision Changes and Hallucinations

Vision Changes and Hallucinations are also common in PD patients, which have been reported to deduct the quality and pace of life [112]. Blurred vision and dry eyes are the initial response towards alteration of vision in PD [113]. In some case alteration in vision occurs due to the dopamine deficiency mediated motor dysfunction [114] and such abnormalities are associated with psychological corners of PD. However, dryness in eye due to less eye blink frequency has been reported to be linked with PD [115]. Such dry eyes phenomenon is also responsible for other vision related complications like itching, burning, seborrheic blepharitis etc. [116,117] PD patients are also reported to have less sensitivity to colour and brightness contrast [118]. In late stage of PD, lack of sharp vision, altered colored vision and impaired ability to read and recognize objects have been reported [118,119].

In a mechanistic explanation, loss of dopaminergic neurons in retina and associated eye structures have been put forwarded [120]. Hallucination is also a reported psychological phenomenon evident in PD pathology [121]. It has been reported that, on an average 20-30% of PD patients, who are under medications, are the frequent sufferers from visual hallucination [121,122]. Most of the cases, hallucination is regarded as the side effect of the medication that, PD patients are taking in advanced stage of PD [121,123]. Misinterpretation of visual objects due to combined effect of medicine and poor vision is the underlying cause of visual hallucination in PD [186,190,191]. Such hallucination can be regarded as the events of peripheral vision, which includes sudden appearance of flash of light, smaller animals and disappearance of objects [124]. In advanced stages of hallucination, PD patients have been reported with the experience of sound and physical sensations, which drags the patient towards a persistent delusion [125]. In case of severe hallucination events in PD physicians are advised to prescribe comparatively lower dose of medicine like donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Razadyne®) or any other antipsychotic drugs [126].

The forerunner report about the incident of hallucination among advanced PD patients was documented in several articles by Goetz and Stebbins [127,128]. While, in the year 1996, visual hallucinations associated with Parkinson disease was reported by Sanchez-Ramos *et al.* [129]. After initial report of visual hallucination by Goetz and Stebbins, succeeding years Inzelberg and colleagues have reported about auditory hallucination [130]. Comparatively, the report on auditory hallucination is very few than visual hallucination, which have been studied and reported by several researchers in succeeding years [131]. In last decade, exclusive work by Pacchetti *et al.* is noteworthy, where the authors have presented a resourceful discussion on the relationship between hallucinations, delusions, and rapid eye movement sleep behavior disorder in PD [132]. Together, the relationship between hallucination and PD pathology is a common fact and it needs care in terms of medical considerations to improve the quality of life of PD patients.

■ Sleeping disturbance

Sleeping disturbance is regarded as one of the most troublesome feature in PD, which reduces the quality of life in PD patients [133-135]. Fragmented sleep due to rigidity or tremor is quite common in among the patients suffering from PD and such situation is also common when none of the PD symptoms are well-enough to recognize [133,136]. Timing of sleep also found to be disturbed in PD patients [133,137]. Some PD sufferers face difficult to sleep at night while, others suffer from drowsiness during day time [104,138]. Dysregulation in the 'sleep-wake' cycle, results into excessive day-time sleep, which could appear long before the expression of characteristic motoric symptoms of neurodegenerative diseases [134,139-141]. Sometimes medication creates destructive dreams or nightmares, which is also a cause underlying sleep disturbance in PD [142].

Rapid eye movement (REM) during sleep is also a feature of sleep disturbance in PD [143]. Moreover, such REM sleep is associated with the muscle activity and as result, the patient with REM sleep never feel sound sleep after acceptable hours of sleeping [133,144]. Regular events of such REM sleep make the patient weak and it has been reported to be a common phenomenon among one third of the PD patients [145]. Moreover, such sleeping disturbances also contribute in the deterioration in the PD pathology by tangling with stress, fatigue and cognitive issues [146]. It is noteworthy that, the incidence of sleeping disturbance can be controlled with the proper medication like clonazepam (Klonopin®), Continuous Positive Airway Pressure device, melatonin supplement etc. [147]. There are several timely articles are there to get an deep insight into the pathophysiology of sleeping disturbance in PD. Chronologically, studies by Factor et al is the pioneer work relating PD pathology with sleep disturbance [148] while, Gagnon and colleagues have highlighted the REM sleep behaviors in PD [149].

Evaluation and measurement of actual scenario of sleeping status in PD got more clear insight with the use 'Parkinson's disease sleep scale', which was used in a study by Chaudhuri and colleague to assessing the sleep and nocturnal disabilities in PD [150]. Several timely reviews have enriched the concept and knowledge on sleeping disturbance in PD among them exclusive work by Larsen *et al.* and Kumar *et al.* and Mahowald are notable for briefing the notion about the association between PD and sleeping disorders [151-153]. However, the links between hallucinations, REM sleep, and PD is a novel concept, which has been hypothesized

by Arnulf and colleagues [153]. Besides sleep disturbance, olfactory dysfunction is also considered as a crucial non-motor symptom, which is having immense importance in PD pathology [154]. Further, it has been reported that, herbal or neurotransmitter replenishment therapy is having promising prospects regarding partial recovery from cognitive and psychological anomalies in PD and other metabolic disorders [155-161]. Together, available literatures clearly pointing out that, non-motor symptoms in PD hold crucial diagnostic possibilities. Further studies are the urgent need of time to establish accurate and rational testing protocols targeting cognitive and psychological anomalies, which in turn could meet the desired early diagnostic promises in PD.

Conclusion

PD is the second most prevalent neurodegenerative disorder classically characterized by motor abnormalities. Available reports are indicating that, the pathophysiology of the disease is not limited within the cardinal features like bradykinesia, resting tremor and postural instabilities; rather, plenty of non-motor symptoms have been recognized in last two decades. Among non-motor symptoms, cognitive impairment and psychological anomalies have been mentioned frequently in several reports (**Figure 1**). The individual, who is going through the pain and sufferings of PD, is the only person can feel the chronic alterations of his/her abilities in terms of cognition, intelligence and psychological status. Most unfortunately, presence of cognitive or psychological abnormalities with or without PD makes the patient a social and economic burden. It is noteworthy that, large scale global organizations are working hand-in-hand to develop the awareness among caregivers about the issue. Research and studies are also in line to highlight various measures and guidelines for the estimation of cognitive impairment and psychological anomalies in PD. However, large scale mass application of such tool still not performed. The association and interlinked crosstalk between cognitive impairment and dementia is another frequently discussed issue in PD perspective, which also provides the deep insight into the pathobiology of PD. In summary, non-motoric features of PD could be a useful tool for the early diagnosis of PD, as those appears far early than the classical symptoms starts to express.

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