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Cognitive Dysfunction in Parkinson's Disease

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1. Introduction

With the progressive improvement in the management of the motor symptoms associated with Parkinson's disease, in the last decades the non-motor aspects of this disorder have gained growing attention by clinical and research communities. Cognitive functioning and its evolution are undoubtedly the most investigated non-motor aspects in PD due to their important implications in the diagnosis and treatment of the disorder as well as in the establishment of the disease functional outcomes. Despite the huge number of studies so far, the nature and the extent of cognitive decline are still poorly understood as well as their relation to disease type, duration and motor features. Heterogeneity has emerged as a key concept when describing the variety of cognitive deficits in PD and the diversity of their underlying neuro-pathophysiological mechanisms (Kehagia et al., 2010; Owen, 2004). Nonetheless, evaluation of the cognitive decline associated with PD is essential for good clinical and pharmacological management of the disease course.

Community-based studies of dementia in patients with Parkinson's disease (PD) have reported prevalence between 28% and 44%. However, longitudinal studies estimating the proportion of patients with PD who will eventually develop dementia reported a 4-year prevalence of dementia of at least 51.6% and an 8-year prevalence of 78% (Williams-Gray et al., 2006). The cumulative incidence of dementia increases with age, with a risk of dementia of 65% by the age of 85 years (Mayeux et al., 1990).

It has been widely assumed that cognitive deficits are only a feature of late-stage PD. Recent studies, however, reveal that subtle cognitive abnormalities that are not clinically apparent, mainly involving the executive functions, occur from the earliest stages of the disease (Foltynie et al., 2004a; Levin & Katzen, 2005) In this regard, two global cognitive profiles have been used to define the type of deficits found in PD, namely mild cognitive impairment and dementia.

The first is an umbrella definition and has been used to characterize the variety of impairments affecting patients without global and extensive cognitive decline. Disorders can involve one or more cognitive domains among which executive/attention, memory and visuospatial are the most common. Usually, mild cognitive impairment is found in the early and middle stages of disease course and is associated with older age at assessment and at disease onset, as well as to male gender, depression and more severe motor symptoms (Aarsland et al., 2011). Dementia instead is more common in the late stage of the disease and is often preceded by early cognitive impairments. It is characterized by a global cognitive

deterioration that involves different domains and which can sensibly lower patients' quality of life. The profile of dementia described in PD is characterized by a subcortical quality (Emre, 2003), similar to dementia with Lewy bodies, and different from Alzheimer's disease (AD; Aarsland et al., 2003; Varanese et al., 2010).

Among the cognitive deficits described, the most well defined are impairments in executive functions. Similarly to those occurring in patients with frontal lesions, these include planning difficulties, inefficient cognitive strategies in problem solving and set shifting, altered goal-directed behavior. These impairments are though to represent a dysfunction of frontostriatal circuitry (Owen et al., 1992). It has been suggested that these two general cognitive profiles might be the behavioral reflections of different pathophysiological mechanisms mediated by distinct neurotransmitters and pathways (chatecholaminergic and cholinergic). In particular, the early deficits are often seen as a consequence of dopaminergic loss and the corresponding modification of the frontostriatal circuitry functioning whereas dementia seems to involve more cholinergic-dependent cortical dysfunction (Kehagia et al., 2010; Owen, 2004).

The etiopathological process underlying the cognitive disturbances in PD, however, is still not completely understood, although several morphological and neurochemical changes are now well recognized.

Alpha-synuclein-positive cortical Lewy body deposition is the key pathological finding in several post-mortem studies (Aarsland et al., 2005; Apaydin et al., 2002; Mattila et al., 2000). In order to avoid including patients with classical Lewy bodies dementia, these studies selected patients that have developed dementia at least 4 years after the diagnosis of PD.

Apaydin and colleagues found that diffuse or transitional Lewy body pathology was the primary substrate in 12 of the 13 patients enrolled in the study (1 patients was excluded due to primary PSP pathology, rather than PD). The mean Lewy body counts were approximately 10-fold higher among the PD patients who developed dementia. Although neocortical Lewy body counts were significantly correlated with the counts of senile plaques and neurofibrillary tangles in this group, suggesting a possible overlapping between these two pathologies, only one patient met the pathological criteria for an „intermediate probability of AD".

Aarsland and colleagues reported similar findings in a post-mortem study involving 22 PD patients, 18 of which diagnosed with dementia. Lewy body was the only pathology observed in demented PD patients, and was significantly associated with the rate of MMSE scores over a period of at least 4 years before death.

The pattern of distribution of Lewy bodies has also been investigated as an important contributor to the cognitive abnormalities observed in PD. Kovari and colleagues found that Lewy bodies density in the entorhinal and anterior cingulate cortices were significantly associated with clinical dementia rating scores, suggesting that Lewy body formation in limbic areas might be crucial for the development of dementia in PD (Kovari et al., 2003). This finding further supports the key role of the Lewy body deposition in the limbic area for the development of dementia in PD.

One of the studies that better clarified the correlation between the cerebral Lewy bodies' distribution and the development of cognitive symptoms in PD is certainly the work from Braak and colleagues (Braak et al., 2005). Their study involved 88 patients diagnosed with PD, who were assigned to one of the six hierarchical stages of PD at post-mortem analysis, based on the topographical distribution pattern of Lewy bodies. The main finding of the

study was the correlation between increasing neuropathological stages and decreasing MMSE score, demonstrating a clear relationship between cognitive impairment and α-synuclein pathology. This specific relationship has also been confirmed in studies involving autosomal dominant forms of PD, were abnormalities in the α-synuclein genotype is associated with early-onset PD with dementia (Farrer et al., 2004; Singleton et al., 2003).

One of the most recent hypotheses suggests that the development of dementia in PD simply represents a shift toward dementia with Lewy bodies, being PD and DLB part of the same disease spectrum whereas the clinical distinction of the two conditions only reflects quantitative and temporal differences in the cerebral Lewy bodies' distribution. Evidence in supports of this hypothesis is provided by some imaging studies. Burton and colleagues have examined the pattern of cerebral atrophy in 57 patients with PD with and without dementia, and compared with controls and patients with Alzheimer's disease and dementia with Lewy bodies. PD patients with dementia were found to have significantly reduced grey matter volume in the occipital lobes bilaterally compared with cognitively intact PD patients, while no volumetric difference was observed between PD patients with dementia and DLB, and significantly less temporal lobe atrophy compared to AD was observed (Burton et al., 2004). Similarly, a study involving single photon emission computed tomography (SPECT) and MRI showed that perfusion deficit in PDD and DLB did not differ, involving in both cases the prenucleus and the inferior lateral parietal regions; this finding was clearly different from the perfusion deficit in the midline parietal region, thus more anterior, observed in AD (Firbank et al., 2003).

The understanding of the pathophysiology of the cognitive disorders in PD derives not only from neuropathological and neuroimaging studies, but also from neurochemical studies. The understanding of neurochemical changes actually provide obvious target for therapeutic interventions. Several neurotransmitter systems have been implicated in the development of cognitive disorders in PD, including dopaminergic, noradrenegirc, serotoninergic and cholinergic.

Dopaminergic deficits have been mainly correlated with executive, visuospatial and fluency deficits (Stern & Langston, 1985; Stern et al., 1990). This relationship is not surprising given that the medial substantia nigra projects to the caudate nucleus, which in turn send input to the frontostriatal circuitry, thought to subserve associative functions (Alexander et al., 1986). However, if dopaminergic deficits do play a major role in cognitive dysfunction in PD, one would expect that levodopa improves these symptoms. Although certain aspects of cognition, like speed information processing and spatial working memory, certainly improve following levodopa therapy (Lange et al., 1992), Williams-Gray and colleagues did not find any major functional impact on the dementia in PD (Williams-Gray et al., 2006) and other functions, like reversal learning, may actually worse (Cools et al., 2001). One possible explanation for the lack of a clear therapeutic benefit from levodopa is that intrinsic factors contribute to the level of dopamine in the prefrontal cortex, not only low level being insufficient, but also very high levels being toxic to the cognitive function. Among these intrinsic factors a major role seems to be played by the catechol-O-methyltransferase (COMT) Va158Met polymorphism. Patients with low-activity COMT genotypes shows increased prefrontal dopaminergic activity and impaired performance in problem solving tasks, with further worsening when the same patients are exposed to levodopa (Foltynie et al., 2004b). Williams-Gray and colleagues also identified that the microtubule-associated protein tau (*MAPT*) H1/H2 gene is an independent predictor of dementia risk (odds ratio =

12.1), with the H1 versus H2 haplotype being associated with a 20% increase in transcription of 4-repeat tau in Lewy body disease brains (Williams-Gray et al., 2009). In their study the *COMT* genotype had no effect on dementia, but had a significant impact on Tower of London performance, a frontostriatally based executive task, which was dynamic, such that the ability to solve this task changed with disease progression. This work suggests that the dementing process in Parkinson's disease is predictable and related to tau while frontal-executive dysfunction evolves independently with a more dopaminergic basis and better prognosis.

The lack of benefit from the levodopa is also motivated by the key involvement of other impaired neurotransmitter systems. While limited evidence exists for noradrenergic and serotoninergic deficits (Cash et al., 1987; Scatton et al., 1983), much stronger evidence exists to support the theory that cholinergic deficits play a major role in the etiology of cognitive deficits in PD. Indeed, cellular loss in the nucleus basalis of Meynert has been demonstrated and associated not only with cortical cholinergic deficits, but also with different levels of cognitive impairment including dementia. (Dubois et al., 1983; Perry et al., 1985). This evidence represents so far the strongest substrate for the treatment approach to the cognitive symptoms in PD.

2. Dysexecutive syndrome

The most common described cognitive deficits in non-demented PD are the impairments in executive functions. In clinical setting, this set of deficits is also known under the term of dysexecutive syndrome. Generally speaking, the main feature of this syndrome is a disruption of goal-directed behaviors that has a negative impact on daily activities especially when patients have to deal with novel situation (Lezak, 1995). In this regard, impairments of executive functions in PD closely resemble the neuropsychological symptoms following frontal lobe lesions, which involve cognitive skills like planning, problem solving, attention shifting, the developing of new and efficient strategies and working memory. This similarity, together with some neuroimaging and pharmacological evidence, suggested that the dysexecutive syndrome in PD might reflect a disruption of the dopaminergic system and of the corresponding frontostriatal circuitry (Kehagia et al., 2010; Owen, 2004). In addition to pure executive disorders, some investigations reported visuospatial and memory deficit that have been often addressed, though, as a consequence of the executive dysfunction (Dubois & Pillon, 1997; Varanese et al., 2011).

The concept of executive functions has a neuropsychological genesis and was introduced to account for a wide range of deficits, classically those associated with dysfunction of the frontal lobe. It postulates the existence of a set of mental skills devoted to the organization and supervision of disparate cognitive processes and to coordinate the exploitation of goal-directed behavior. Executive functions are thus fundamental for an individual to engage successfully in purposive, self-serving behavior. Such a high-level control is needed in daily life, especially in those situations in which the automatic and habitual behavior does not adequately fit the context demands. For instance, executive functions are recruited when a person has to face novel problems (e.g. learning to ride a motorbike), when has to override the interfering effects of irrelevant information (e.g. paying attention to the road despite the surrounding landscape) when mental planning is necessary before action execution (e.g. deciding which way to go at a crossing) when attention is divided among multiple tasks (e.g. talking at the phone while driving) when the individual has to prioritize among

different goals (e.g. which move comes first in a chess game). Even if largely investigated, there is an extensive theoretical debate on the nature and number of executive processes. The first issue is whether a unique and single definition of executive functions can account for the variety of disorders associated with executive disruption. Different theories(Norman & Shallice, 1986) postulate the existence of a single high-level executive process that controls and organizes the functioning of lower level abilities in the service of the ongoing task. In the model proposed by Norman and Shallice (1986) for instance, the "supervisory attentional system" is responsible for the biasing of "schema" which can be roughly described as more routine and automatic behaviors. Baddeley and Hitch (1986) on the other hand, proposed the Working Memory model that consists of a high-level central executive component and a set of lower level subsidiary memory storages and buffers.

Differently from these models, executive processes might be also though as a set of distinct and partially independent skills that could be specifically recruited on the basis of task-goals. This set includes some cognitive abilities like flexibility and set shifting, complex motor programming, planning and problem solving, and self-monitoring.

The theoretical debate about the nature and number of executive functions (single versus multifaceted system) acquires a particular importance when assessing the dysexecutive syndrome in PD. A number of studies have reported dissociation between distinct executive components affected by PD as well as dissociation between low- and high-level functioning deficits. Even more interesting are the data showing that the extent of executive impairments and the cognitive domain involved might vary as a function of motor disorder (Owen, 2000). For instance, when tested with a spatial working memory task, medicated and non-medicated patients performed differently, with only the former showing significant deficits (Owen et al., 1992). Furthermore, it has been found that a group of PD patients showed impaired performance at spatial working memory test while normal performance in verbal working memory task (Bradley et al., 1989).

In the attempt to characterize this variability, some authors got to the conclusion that executive deficits associated with PD could be better described in terms of the involvement of high- versus low-level functioning that, in turn, seems to be related to the disease progression. Specifically, it has been suggested that high-level processing dysfunction might occur earlier during disease course, whereas impairments of low-level processes are associated with later stages of PD. Some results from a set of studies using verbal and spatial working memory tasks come in support of this hypothesis (Lewis et al., 2003a; Lewis et al., 2003b; Owen et al., 1993; Owen et al., 1992). Owen and colleagues manipulated the degree of attentional control involvement by varying some basic characteristics of a spatial task. In a first version of the test, in order to place selectively significant demands on memory processes, the authors had patients with PD remembering sequences of color-changing boxes presented on a computer screen. In a second version of the task, subjects were presented with a number of colored boxes and instructed to search for blue tokens hidden inside some of these boxes. An important rule was to avoid boxes in which a token was already found. Similarly to the first version this task involves spatial memory processes. However, in addition to that, it also recruits attentional control needed for the active manipulation and reorganization of relevant contents held in working memory and for the development of efficient searching strategies. Notably, the authors revealed important differences in the performance among patients and between tasks, which correlated with disease stages. In particular, medicated subjects who were experiencing more severe clinical

symptoms performed poorly at the first task in which low level of attentional control was required. At the same test, patients with mild disease, who were either medicated or non-medicated, performed normally. However, these groups' differences disappeared when subjects were tested with more complex spatial search task. Medicated patients with either severe or mild disease performed poorly as compared to control. In addition, the non-medicated patients showed a trend toward impairment (Owen et al., 1993; Owen et al., 1992).

The distinction between low- versus high-level processing involvement is crucial for the understanding of the possible pathological mechanisms underlying PD cognitive decline and for the identification of the corresponding neural substrates. Several studies, have suggested that low and high-level processes might recruit partially distinct anatomical areas within the brain, and in particular within the prefrontal cortex. In normal subjects, PET and fMRI investigations revealed that the active manipulation of working memory contents as well as the identification of strategies based upon task goals load on the mid-dorsolateral frontal cortex. On the other hand, lower level functioning such as encoding and retrieval of information engage more ventral frontal regions (Owen, 2000).This evidence led to the description of the lateral frontal cortex as separated in two distinct systems, each supporting different aspects of executive processing in connections to posterior association areas. Briefly, the ventrolateral frontal cortex is the first station through which information coming from posterior regions accesses the frontal lobe to be integrated for further processing. It is thus considered to be critical for a variety of low-level memory processes. Conversely, the mid-dorsolateral frontal cortex is assumed to be a second-step station responsible for higher processes such as manipulation and monitoring of information held in memory. Based on this evidence, the dissociation between high- and low-level types of impairment seen in PD might reflect a different involvement of the two regions within frontal cortex during the disease progression. It is likely that PD might affect early a specific component of the executive system that is the one requiring attention control and that involve the mid-dorsolateral area. On the other hand, dysfunction of the ventrolateral cortex and, in turn, impairments of more basic mnemonic processes, might occur late in the pathology in parallel with the development of more severe motor symptoms.

Taken together, these findings point at the frontostriatal circuitry as a probable pathophysiological mechanism underlying the cognitive deficits in PD. The different anatomical and cytoarchitectonical prefrontal regions receive fibers from the distinct regions of the basal ganglia in a highly topographical manner (Alexander et al., 1986). It has been suggested that the executive impairments in PD might be a consequence of the interruption of the normal flow of information through these frontostriatal "highways" owe to the dopamine depletion associated with the disease. The dissociation between low and high-level executive impairments and the parallel progression of cognitive and motor symptoms reflect the spatiotemporal progression of dopamine loss in the striatum, which progressively affects distinct regions and their afferents to different frontal areas. Besides the frontostriatal circuitry, also the dopamine depletion within the prefrontal cortex itself might play an important role in the pattern of executive disorders observed in PD (Scatton et al., 1983)

The dopamine-dependent hypothesis has been put under investigation with a number of studies. First, it has been shown that dopaminergic enhancement has a restorative effect on a variety of executive processes such as flexibility during problem solving task, attention switching (Cools et al., 2003), working memory (Costa et al., 2009; Lewis et al., 2005) and

response inhibition (Gauggel et al., 2004). However, on the other hand, dopaminergic restoration has been associated with worsening of performance on a set of cognitive processes mainly involving feedback related learning. For instance dopaminergic overdose has been linked to increased impulsivity and abnormal betting in a gambling setting (Cools et al., 2003). Moreover, differently from unmedicated patients, subjects under dopaminergic treatment showed impulsive responding and failure to switch to a newly rewarded stimulus when the currently selected one is no longer associated with reward (reversal learning). The dual opposite effects of dopamine enhancement on cognitive functioning has been interpreted as a reflection of the different degree of dopamine depletion among the striatal regions. In fact, whereas dopaminergic dosing for adequate treatment of motor symptoms restores striatal dorsal regions functioning and ameliorates high-level cognitive processes, conversely it has deleterious effect on cognitive functions depending on less depleted striatal regions (ventral) and on the corresponding cortical projections (orbitofrontal cortex).
Besides these pharmacological studies, PET and fMRI works have investigated the contribution of the frontostriatal circuitry to PD executive impairments by examining the patterns of cortical and subcortical activations during executive tasks (Dagher et al., 2001; Lewis et al., 2003a; Mattay et al., 2002). The obtained results are inconsistent in terms of the specific frontal versus striatal contribution. However, besides those differences that are probably due to methodological issues, they generally confirmed the important role of the dopamine depletion in cognitive impairments associated with PD and the distinction between high and low level executive processes. These are to key concepts and have important implications in the neuropsychological evaluation of the dysexecutive syndrome in the daily practice.

3. Neuropsychological assessment of the dysexecutive syndrome

As previously reported, there is still a lack of consensus on a clear definition of executive functions. Some theories postulate the existence of a single system in which a putative central attention process coordinates and organizes the ongoing behavior by controlling low-level and subsidiary skills. On the other hand, executive functions have been described as set of partially independent, high-level functions that can be singularly disrupted by either selective lesions or system disease. As consequence of this theoretical debate, developing clinical instruments able to assess deficits of the executive functions have proved to be very difficult.
Nonetheless, when executive functions have been investigated in the normal population through a variety of tests, large individual differences were found, even within the same executive tasks. In addition, the weak correlations observed among individual performance at different executive tests suggested that the underlying cognitive processes might share little variance (Miyake et al., 2000a; Spitoni et al., 2002). These data have been generally interpreted as a convincing argument in favor of a separation of executive components, leading also to a revision of the "unique" system theories (Baddeley, 1996; Carlesimo et al., 2001; Klauer & Zhao, 2004).
This probable separation of executive components must be taken into account during neuropsychological evaluations in daily practice. In order to assess adequately executive functioning, a multidimensional approach seems to be fundamental. In this regard, there is need of tools able to scan and tap a variety of distinct abilities and capable of detecting the complexity of executive system (in terms of low- versus high level functioning). However, as pointed out by some authors (Miyake et al., 2000b), many of the classical executive tests adopted for clinical evaluation, do not have clear construct validity and seem to measure

different skills at the same time. For instance, the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993) measures "mental set shifting" and the associated tendency to perseveration, "problem solving" and "abstract reasoning" abilities. In spite of the real difficulty to distinguish between the different capacities required to solve its demands, this test continues to be used as a measure of executive functions. Similarly, the Tower of London test (TOL; Shallice, 1982), is thought to be sensitive to a variety of impairments among which are "attention, "problem solving", "planning" and "cognitive inhibition" deficits.

Traditional executive tests have been used to investigate the dysexecutive syndrome in PD. Patients who do not have a global cognitive dysfunction showed poor performance when tested with the WCST, the Trail Making test (TMT) and the TOL (Bowen et al., 1975; Hietanen & Teravainen, 1986; Owen et al., 1992; Perfetti et al., 2010; Varanese et al., 2011; Vingerhoets et al., 2003). For instance, when compared to age matched control subjects, patients with PD showed poorer ability to find new categories (Varanese et al., 2011; Vingerhoets et al., 2003) in the WCST and a greater tendency to perseverate (Perfetti et al., 2010), lesser planning skill at the TOL (Owen et al., 1992; Perfetti et al., 2010). Verbal fluency and visuospatial memory also resulted impaired (Cooper et al., 1991; Owen et al., 1992) as well as inhibition of response (Petrova et al., 2010).

However, in light of the considerations mentioned above these traditional instruments might not be capable in detecting and precisely characterized the type of dysexecutive syndrome associated with PD. The first argument in favor of this hypothesis is that the traditional instruments might fail in distinguishing between different executive components as they often tap a variety of executive abilities without a clear distinction between them and between high and low-level functioning. In fact, based upon the results showing that high-level functioning might be early impaired in PD, performance at traditional tests might be globally disrupted by such a condition. Second, the presence of everyday problems in dysexecutive patients may not (necessary) fit with the scores resulting from a structured testing assessment like that provided by traditional measures. It has been reported that individual patients could perform well on these measures even if showing obvious and deleterious symptoms in less structure environment, suggestive of a more complex disorganization of everyday behavior (Eslinger & Damasio, 1985; Shallice & Burgess, 1991). In traditional neuropsychological testing, since instructions are explicit and task initiation is prompted by the examiner, success may be highly characterized which, in turns, might cause a failure in detecting executive dysfunction (Burgess et al., 2006). In order to overcome the limits of traditional executive measures and put the hypothesis mentioned above under investigation, we recently adopted an ecological neuropsychological battery to assess executive dysfunction in PD. Specifically, we administered a set of traditional executive tests and the Behavioral Assessment of Dysexecutive Syndrome (BADS; Wilson et al., 1996) battery to a group of non-demented PD patients and a sample of demographically matched control subjects. The BADS was purposely developed with the intent of measuring a wide range of executive impairments and to predict everyday problems (ecological approach) by assessing capacities that are normally involved in everyday activities through six different subtests. Moreover, the BADS takes into account the complexity of the high-level executive functioning by loading onto organizational skills and task-goals management capabilities. It requires participants to plan activities over long time intervals and, most importantly, to prioritize among competitive demands. Taken together these features make the BADS a less structure test (open-ended) and thus a good candidate for detecting subtle executive disorders associated with PD.

The results obtained in our study support the use of such a multidimensional approach. We showed that the PD sample generally performed less well then control subjects in almost the administered tests. However, when we compared the sensitivity of the different adopted tools in predicting group membership, we revealed that the BADS total score and the "modified six elements" sub-score were the best predictors. Figure 1 summarizes part of the results. The figure displays the executive tests' z-scores of the PD sample computed on the basis of normal subjects' performance.

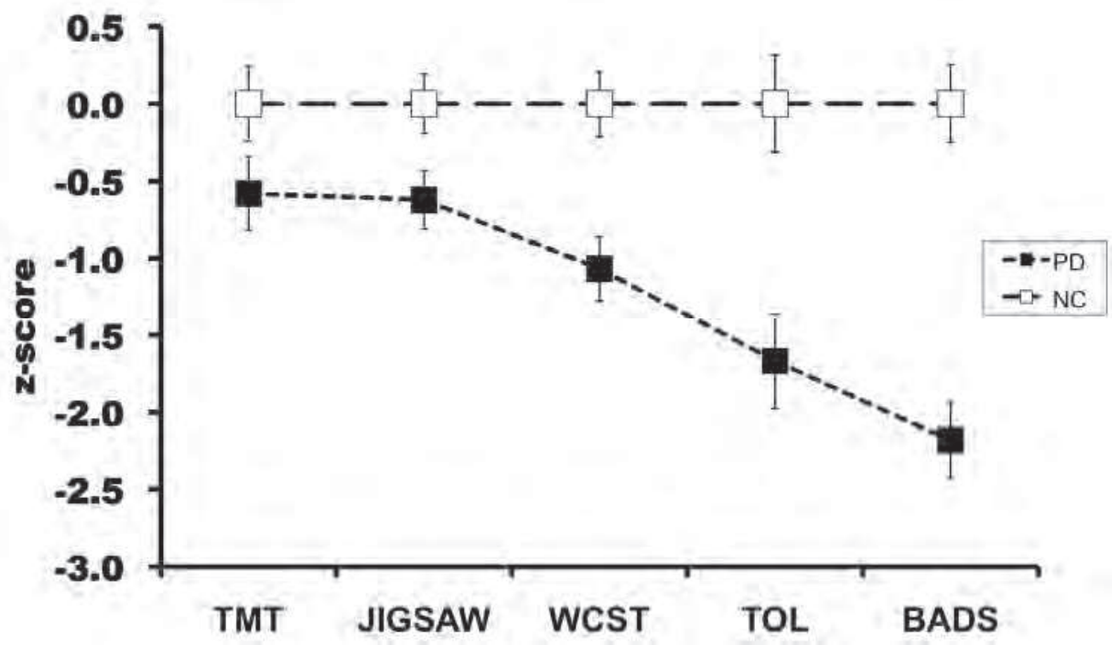


Fig. 1. Profile plots of the Z scores at the different administered tests, computed on the basis of normal subjects' performance. TMT, Trail Making Test; WCST, Wisconsin Card Sorting Test; TOL, Tower of London Test; BADS, Behavioural Assessment of the Dysexecutive Syndrome; JIGSAW, Jigsaw Puzzle Test; PD, Parkinson's Disease; NC, Normal Control

These results are in agreement with the hypothesized distinction between low- and high-level executive functioning in PD. The modified six elements subtest is a task that makes strong demands on the high-level functioning. Subject has to plan, organize and monitor the ongoing behavior over long period of time while concurrently remembering and carrying out a specific goal. It is an open-ended (less structured) task that strongly loads on subject's organizational skills making it sensitive to the disruption of goal-directed behavior. These results support and bolster the idea that, in early PD, impairment of executive functioning mainly involves the high attentional control causing a loss of the organizational skills. In addition, they support the use of a multidimensional approach during neuropsychological evaluation of patients with PD.
Evidence in line with these conclusions comes from an investigation conducted by Varanese and colleagues (2010). The authors were interested in studying the relation between apathy and cognitive profile in non-demented individuals with PD. The study is a good example of a multidimensional approach through the use of traditional executive tests. Apathy was associated with the presence of executive disorders that was detected and characterized by the identification of an underlying core deficit among the different administered tests (see table 1

for partial results). The authors reported that apathy patients showed a selective deficit in the free recalling of words at the California Verbal Learning Test (CVLT-II; Delis et al., 2002) and poor ability to find new categories at the WCST. Rather than a primary memory disorder the low score in free recalling was interpreted as an impairment of poor strategy implementation at the encoding and recalling stages. This interpretation was supported by the fact that, in the CVLT-II, the words to be retained can be more efficiently encoded and recalled by using a semantic strategy. Moreover, the lower number of categories identified by the apathetic patients at the WCST bare this conclusion. In summary, the main impairment associated with apathy in PD involved the ability to abstract reasoning and developing new strategies for the accomplishment of task goals. In other words PD patients were affected by a disruption of organizational skills and goal-directed behavior.

Domain	Test	Measure	PD-A	PD-NA	Sig.
recall	CVLT-II	**total free recall**	**22.8 (5.8)**	**28 (3.7)**	**0.000***
	CVLT-II	**short delay free**	**5.9 (2.3)**	**7.4 (1.2)**	**0.001***
	CVLT-II	**long delay free**	**5 (2.2)**	**7.2 (1.5)**	**0.000***
	CVLT-II	**long delay cued**	**5.1 (2.1)**	**7.4 (1.9)**	**0.000***
recognition	CVLT-II	**delayed recognition**	**8 (0.8)**	**8.6 (0.6)**	**0.01***
learning	CVLT-II	total learning slope	3 (1.2)	2.8 (1.1)	0.55
attention	D-KEFS	visual scanning	35.9 (17.4)	33.2 (12.4)	0.5
	Dsy		44.9 (16.5)	51.4 (15.2)	0.08
speed info processing	D-KEFS	number sequence	0.4 (0.9)	0.3 (0.5)	0.6
		letter sequence	0.6 (1)	0.2 (0.4)	0.1
		motor speed	52.4 (32)	45 (22.5)	0.6
executive functions	WCST-64	**total correct**	**34.9 (10.8)**	**45.6 (11.2)**	**0.000***
		perseverative responses	14.9 (7.9)	12.1 (11.5)	0.33
		categories completed	**1.6 (1.3)**	**3.2 (1.7)**	**0.000***
	D-KEFS	number-letter	2.5 (1.5)	1.7 (1)	0.09

P <0.05, FDR corrected. D-KEFS=Delis-Kaplan Executive Function system; CVLT-II=California Verbal Learning Test–II; WCST-64= Wisconsin Card Sorting Test-64 cards version; DSy= Digit symbol

Table 1. All values represent mean (SD). Between-groups comparisons have been investigating using univariate analysis of variance for each variable, with age, disease duration and Led as covariates and group membership (apathy vs. No apathy) as fixed factor (ANCOVA).

4. Dementia

Dementia in patients with Parkinson's disease (PDD) is usually defined as a subcortical pattern of cognitive impairment (i.e. deficits in attention, executive functions, visuospatial and constructional abilities), where the core features is represented by an impairment of cognitive functions, that leads to deficits in planning, sequencing, execution of goal-direct behavior, and typically in the maintenance of new sequence patterns after the shift from a previously learned sequence of movement (Emre, 2003). Memory is also impaired, with prevalent involvement of working and episodic memory, and procedural learning (Pillon et al., 1993) but differently from the amnesic syndrome of AD, these deficits in PD lies in retrieval rather than storage of information. Although also described in other forms of dementia, visuospatial impairment is more severe in PDD patients (Huber et al., 1989), and it has been suggested that impaired performance in visuospatial tasks may be related to problems with sequential organization of behavior, thus expressing a frontal executive dysfunction rather than pure parieto-occipital pathology (Stern et al., 1983). Attention is compromised with presence of attentive fluctuations (Ballard et al., 2002).
Psychotic symptoms are frequently associated with dementia in PD, with a prevalence ranging between 25 and 30% (Ravina et al., 2007). Visual hallucinations are the most prevalent manifestation of psychosis, and they can range from simple illusions or flashes of light or vague feelings of presence or passage of humans and animals, to the complex formed visions of animals and people more commonly observed.
Hence, PDD can be difficult to discriminate from DLB, and the temporal course is the main distinction.

4.1 Cognitive fluctuations

As previously discussed it has been hypothesized that subgroups with different cognitive profiles exist within PDD, suggesting that frontosubcortical changes are the main contributing factor for dementia in some patients while, in others, cortical and hippocampal changes may predominate (Aarsland et al., 2003). Varanese and colleagues identified the occurrence of cognitive fluctuations (FC) as the clinical variable associated with a DLB pattern of impairment in PDD. This study enrolled 27 PDD, 33 DLB, 18 AD patients and 20 healthy control subjects. Based on the presence or absence of FC, PDD patients were divided in two subgroups and their performance at the Dementia Rating Scale 2 (DRS-2) was compared with the performance of the other groups. The authors found that PDD patients with FC had a pattern of cognitive impairments similar to DLB, which involved prevalently the attention and initiation/perseveration domains, and which was significantly more pronounced compared to the pattern exhibited by PDD patients without FC (Varanese et al., 2010).
FC is described as an interruption in the ongoing flow of awareness or attention that impacts on functional abilities and appears as a fluctuation in the level of arousal and cognitive performance (Bradshaw et al., 2004; Serrano & Garcia-Borreguero, 2004), and it is also known to be associated with episodes of disturbed consciousness. Byrne and colleagues reported the case of one patient who had day-to-day changes of the MMSE, and the case of another patient who experienced confusional episodes that varied from being mute and unable to stand without assistance to being capable of carrying on a conversation (Byrne et al., 1989); Gibb and colleagues described episodes of stupor in a patient affected by DLB who appeared alert and responsive to commands out of these episodes (Gibb et al., 1987).

The most widely used instrument to detect the FC in the clinical setting is the Clinician Assessment of Fluctuation scale (CAF) (Walker et al., 2000a). This is a short scale developed to provide a quantitative score of the FC, based upon the clinician's interpretation of caregiver responses to the two key items that made up the scale: "Does the patient ever have spontaneous impaired alertness and concentration –i.e. appears drowsy but awake, looks dazed, is not aware of what's going on?" (clear examples demonstrating impaired consciousness with variations in performance/cognition are required to receive a positive rating); "Has the level of confusion experienced by the patient tended to vary recently from day to day or week to week? For example, becoming worse, then perhaps improving for a while?" (significant fluctuation is regarded as present if distinct examples of differences in performance/cognition can be given on at least two occasion over the month). If a positive rating of FC is present (two positive answers to question 1 and 2), a severity rating should be made on a 1 to 4 scale for the frequency of FC (where 1 = ≤ 1 per month, 2 = monthly-weekly, 3 = weekly-daily, 4 = ≥ daily), and on a 0 to 4 scale for duration of FC (where 0 = seconds, 1 = ≤ 5 minutes, 2 = 5 minutes-1 hour, 3 = ≥ 1 hour, 4 = ≥ 1 day). The two partial scores (frequency and duration) are multiplied together to produce a severity score from 0 to 12, 0 representing no fluctuating cognition, and 12 representing severe fluctuating cognition (a score of 16 would signify a continuous clouded state, which, by definition, would denote no fluctuation).

Bradshaw and colleagues showed that item one of CAF ("does the patient ever have spontaneous impaired alertness and concentrations – i.e. appears drowsy but awake, looks dazed, is not aware of what's going on?") is not enough specific in detecting FC in DLB, as AD caregivers response is often positive; but verbatim descriptions of FC in DLB have particular qualitative characteristics that differ from those obtained in AD patients: DLB caregivers frequently provided descriptions that suggested a lapse in the stream of awareness or attention reflecting that patient lost the ability to engage in meaningful cognitive or physical activity, while AD caregivers described periods of confusion characterized by repetitiveness in conversation or forgetfulness in relation to a recent event as a result of memory failure (Bradshaw et al., 2004).

Qualitative caregiver's description provides clear differences in the nature of the FC.

In our personal case study, caregivers usually described FC as a lapse in the stream of awareness or attention, sometimes reflecting confabulatory or delusional quality (17 patients, 89,47%: "sometimes he seems to be blank, and I must shake him to have a response", "she seems to be drowsy", "she seems to be confused", "he has temporary lapses and can't focus properly", "he seems to have some black out", "sometimes she says something senseless, than suddenly come back clear", "he seems to be not aware of what is around him", "he cannot concentrate on what he is doing", "she detaches", "sometimes he says that there are extra people staying at home, than he comes back clear", "sometimes we can talk over with him, sometimes doesn't understand a word"); only in two case (12.51%) FC appeared as episodes of forgetfulness ("sometimes she cannot find something at home because she don't remember where she put it, so she wonder around confused"; "some days he asks me the same question 10 times in 10 minutes"). The caregiver provided descriptions of the FC that reflected deficit in attention or awareness in a significant percentage of cases ($p<0.001$).

The evaluation of FC in the diagnosis of DLB causes the greatest difficulty in clinical practice because assessment methods, as the CAF largely rely on clinical experience and inter-rater

reliability is reported to be low (Litvan et al., 1998; Mega et al., 1996). Furthermore it is frequently difficult for raters to reach agreement on differentiating episodes of mild fluctuation in consciousness from diurnal hypersomnia, frequently observed in dementia (Lopez et al., 1999).
The EEG is a useful tool to detect FC, providing a measure of cortical arousal useful to define and stage levels of human awareness as well as levels of variability in the frequency of cortical rhythms. At the EEG FC are represented as slow activity and epoch-by-epoch fluctuation in the mean frequency (Barber et al., 2000; Briel et al., 1999; Onofrj et al., 2003; Walker et al., 2000b). In a study focused on EEG in AD, DLB and PDD, Bonanni and colleagues have recently shown that around 20% of PDD patients at onset exhibit FC and that only those with FC displayed the EEG alterations typically observed in DLB (pre-alpha activity and variability in the mean frequency), but the rate of PDD exhibiting FC significantly increased after two years of follow up (Bonanni et al., 2008).

5. Therapeutic management

The pharmacological management of the cognitive symptoms represents a major challenge e in PD.
Due to the paucity of evidence-based therapeutic options, the traditional approach has been widely based on withdrawal of medications known to worse the cognitive functioning. Any attempt should be made to avoid benzodiazepines and anitmuscaric antidepressants. Antiparkinsonian medications are also know to affect the cognitive functions and a gradual withdrawal should be considered for those medications with higher cognitive adverse effect but lower motor benefit, like anticholinergics, amantadine, selegiline and eventually dopamine-agonists.
Another important step, when dealing with a patient presenting with symptoms of confusion, is to exclude all the identifiable and removable triggering factors. The most frequent of these occurring in PD patients are concomitant infections, dehydration, subdural hematoma and electrolyte imbalance. Their treatment often is sufficient to improve the cognitive worsening.
There is now emerging evidence to support the efficacy of a specific class of drug, originally developed as a treatment for Alzheimer's disease: cholinesterase inhibitors.
These drugs enhance the cholinergic transmission by preventing the catabolism of acetylcholine released in the presynaptic neurons. The use of these compounds is certainly justified by the key role of disruption of the cholinergic system among the neurochemical changing involved in the development of dementia in PD, as discussed previously.
Rivastigmine, donepezil and galantamine are the three drugs of this class available, and they have different pharmacological properties that may reflect a different profile of efficacy and safety. It is well known, for instance, that rivastigmine inhibit both the acetylcholinesterase and the butirrylcholinesterase, leading to a greater efficacy (Poirier, 2002).
The beneficial effect of cholinesterase inhibitors, particularly donepezil and rivastigmine, on the cognitive function was originally suggested in preliminary open label studies, without any associated significant deterioration in motor function in the majority of the patients.
In more recent years evidence from large placebo-controlled trials conducted on rivastigmine and donepezil further highlighted the safety and efficacy of these compounds.

5.1 Rivastigmine

Rivastigmine was investigated in the "Exelon in Parkinson's Disease Dementia Study"(EXPRESS). This 24-week study involved 541 patients randomized to receive either rivastigmine or placebo in a double blind design. As per inclusion criteria patients had to be diagnosed with PD according to the UKPDS criteria and developed dementia at least 2 years after the diagnosis of PD, in order to reduce the chance of including patients with Lewy bodies disease. The rivstigmine dose ranged between 3 and 12 mg/day. The primary outcome measures of the study were the Alzheimer's disease Assessment scale (ADAS-cog) and the Alzheimer's disease Cooperative study – Clinician's Global Impression of Change (ADCS-CGIC). Although the improvement in the ADAS-cog was very modest (2.1 points in 70-point scale) in the rivastigmine group, the placebo group worsened of 0.7 points leading to a significant difference between the two groups ($p<0.001$). The improvement in the ADCS-CGI was, instead, clinically meaningful in 19.8% of patients receiving rivastigmine compared to 14.5% of patient receiving placebo ($p=0.007$). Hence rivastigmine produced a clinically relevant improvement in almost 20% of patient.

The drug was well tolerated, with 72.7% of patients completing the study. The adverse events were predominantly cholinergic and, among these, nausea was the most frequent one occurring in the 29% of patients. Although the UPDRS motor score did not significantly change at the end of the study, 27% of patients in the rivastigmine arm reported worsening of parkinsonian symptoms. Due to the limited duration of the trial data on safety and tolerability are certainly limited, although the 24-week open label extension study has not shown further safety and tolerability issues (Emre et al., 2004).

5.2 Donepezil

Donepezil was investigated in two small placebo-controlled trials.

The first trial involved 14 patients randomized to receive either donepezil 5-10 mg or placebo for 10 weeks in a double blind crossover design. The investigators reported an improvement of 2.1 scores in the MMSE compared to the placebo group ($p=0.013$), with no change in the UPDRS scores at the end of the study. However, although this trial suggested that donepezil can improve cognition in patients with PD without worsening of motor function, the study results are limited by the small sample size and by the crossover design, as no washout period was allowed between the two stages of the trial (Aarsland et al., 2002).

The second study involved 16 patients randomized to receive donepezil 2.5-10 mg or placebo for 18 weeks. This study showed improvement in only one outcome measure, the dementia rating scale, in the donepezil arm compared to the placebo arm (p0.03), however the improvement consisted in less than 3 points on a mean score of 22, thus the clinical meaningfulness of this change is very limited. Furthermore the study raised concerns about the tolerability of the drug, which was limited to a mean dose of 6.4 mg/day (Leroi et al., 2004).

In conclusion, rivastigmine should be the first-line cholinesterase inhibitor in patients with PD and dementia, as it is the only agent supported by evidence from a large scale randomized controlled trial.

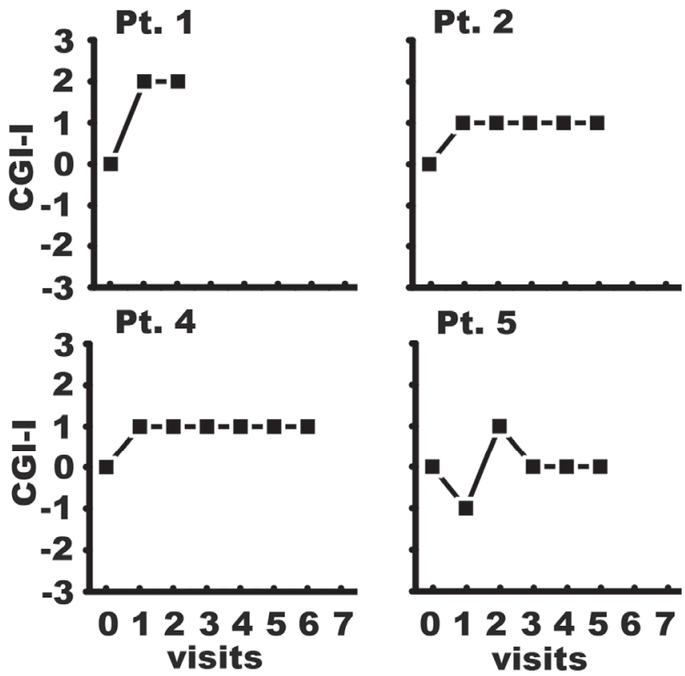
5.3 Wakefulness-promoting medications

Modafinil and armodafinil are central nervous system stimulants, which exert their effect through activation of the orexin-containing neurons in the hypothalamus, prefrontal cortex and anterior cingulate cortex.

Modafinil has been shown to ameliorate excessive daytime sleepiness in patients with Parkinson's disease (Adler et al., 2003) as well as wakefulness, vigilance and attention in narcolepsy (Hirshkowitz et al., 2007) and in healthy volunteers (Wong et al., 1999). Modafinil has been associated with improvements in cognitive performance in healthy volunteers and in patients with attention-deficit hyperactivity disorder and schizophrenia, implying that it may be useful in cognitively impaired patients with PD with or without associated daytime sleepiness.

We have been investigating the use of waking-promoting agents (modafinil and armodafinil) as treatment for FC and cognitive dysfunction typical of PDD/DLB in two preliminary studies.

In a retrospective observation conducted in a group of six PDD patients who received modafinil or armodafinil for excessive daytime sleepiness and showed concomitant improvement in their cognitive skills. The evaluation was conducted through CGI scales (severity-S and improvement-I) extracted by two independent raters based upon the treating physician notes over a follow up period ranging between 18 and 66 months. The inter-rater reliability reached a kappa measure of 0.69. Four patients with stable medications over the follow up period were included in the final analysis, while three were excluded due to concomitant use of cognitive enhancers or other medications that could potentially have an impact on cognitive abilities. All the four patients showed improvement in their cognitive status that translated in improved social interactions and that was sustained over the entire follow up period. Interestingly, the greatest improvement was observed in those patients with more compromised cognitive status at baseline. The figure below summarizes the improvement observed:



The interval between visits is six months.

Fig. 2. CGI-I ratings: 3=very much improved; 2=much improved; 1=minimally improved; 0=no change; -1=minimally worse; -2=much worse; -3= very much worse.

Based on the retrospective observation, we have collected preliminary behavioral data in a sample of 9 patients with PDD on their pre- and post-dose performance at vigilance and attention-computerized tests. For this one-day experiment, the patients received armodafinil 150 mg, and were tested twice, before and after the dose. They had to perform two different computerized tests, whose main outcome is reaction time (RT). The first test is a detection task assessing exogenous attention, in which the patient has to respond quickly to the appearance of a stimulus on the left or right side of the pc screen that can be either or not preceded by a brief blinking image (match or non-match trial); the second test is a classical psychomotor vigilance task (PVT), based on simple cued reaction time, in which the patient has to stop a counter appearing at random intervals on the pc screen. A preliminary analysis of the individual performances pre- and post dose showed that administration of armodafinil is followed by reduction in RT in both the detection task and the PVT; furthermore in the post-dose performances there is a consistent and relevant decrement in the standard deviation, which we consider a marker of cognitive stability during the test, thus reflecting a reduction in spontaneous fluctuations of attention occurring during the test performance. As in the case of the clinical series described above, we observed the greatest effect of armodafinil in the more cognitively compromised patient (pt. 2): this patient greatly improved in the PVT performance (she was unable to perform the detection task due to fatigue at baseline). The table below provides an example of patients' performance before and after the drug (means are expressed in milliseconds):

				pre-dose			post-dose		
Pt	**age**	**MMSE**	**DRS-2**	**detection match mean RT (SD)**	**Detection nonmatch mean RT (SD)**	**PVT mean RT (SD)**	**detection match mean RT (SD)**	**Detection nonmatch mean RT (SD)**	**PVT mean RT (SD)**
1	88	26	121	420.46 (149)	423.48 (150.57)	531.87 (250.77)	399.97 (123.02)	407.73 (133.60)	516.82 (191.29)
2	78	19	94	NA	NA	736.02 (364.56)	NA	NA	627.12 (292.74)
3	76	24	119	464.4 (191.58)	468.08 (130.90)	351.24 (90.24)	392.34 (96.09)	423.51 (110.37)	328.25 (70.11)

6. Conclusion

Contrary to James Parkinson's original description that intellect was preserved, it is now clear that subtle cognitive deficits occur in PD from the earliest stage of disease and a substantial proportion of patients eventually develop dementia. Although the underlying pathophysiology is not fully understood, evidence from post-mortem, neurochemical and neuroimaging studies suggests that the altered mechanisms leading to dementia in PD are similar to those described in DLB. Most likely the two syndromes represents a continuum within the spectrum of the alpha-synuclein pathology.

Early cognitive impairment, mainly in the form of dysexecutive syndrome, occurs in a significant proportion of patients even in the early stages of disease. The evaluation of this cognitive change represents a major challenge in the clinical setting, as traditional neuropsychological tools may fail to detect the subtle impairments even when they clearly impact on the patient's quality of life by decreasing the pre-disease executive abilities. More

ecological instruments, able to characterize patient's executive behavior in a less structured environment and closely resembling the daily routine, may provide a key contribution to the early detection of the dysexecutive syndrome in PD. Recognizing patients with dysexecutive syndrome may have important prognostic implications. It has been suggested, indeed, that the frontal-executive dysfunction evolves independently from dementia, relies on a more dopaminergic basis and has a better prognosis.

The underlying mechanisms of overt dementia in PD are still poorly understood. It is well established, however, that clinical manifestations of dementia in PD resemble very close the peculiarity of DLB. Among his cognitive fluctuations represent one of the core symptoms, with their frequency and severity progressively increasing during the course of the disease.

The most obvious therapeutic strategy in the treatment of dementia associated with PD is to target the cholinergic deficits. The available evidence, although limited, suggests that cholinesterase inhibitors may have a dual efficacy in ameliorating both cognitive and behavioral symptoms. However, their tolerability seems variable, with peripheral cholinergic adverse events often preventing therapeutic doses being reached. Due to the proposed mechanism of altered activation system, wakefulness promoting medications, like modafinil and armodafinil, may be able to improve cognition by improving alertness and certainly warrant more extensive investigations to determine their beneficial role in the treatment of dementia in in PD.

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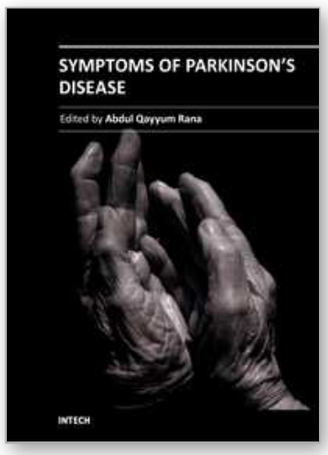

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This book about Parkinsonâ€™s disease provides a detailed account of various aspects of this complicated neurological condition. Although most of the important motor and non-motor symptoms of Parkinsonâ€™s disease have been discussed in this book, but in particular a detailed account has been provided about the most disabling symptoms such as dementia, depression, and other psychiatric as well as gastrointestinal symptoms. The mechanisms responsible for the development of these symptoms have also been discussed. Not only the clinicians may benefit from this book but also basic scientists can get enough information from the various chapters which have been written by well known faculty.

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