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Correlates of excessive daytime sleepiness in Parkinson's disease

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Abstract

Measures of excessive daytime sleepiness, neuropsychologic function, and mood were assessed in twenty-two persons with mid-stage Parkinson's disease (PD) and sixteen age-matched healthy controls. Levodopa dose equivalents (LDE) were computed for the patients. While Epworth sleepiness score (ESS), Mini Mental State Exam, logical memory, Stroop, and the mood scales, reliably distinguished patients from controls, only the mood scales (especially anxiety) were reliably associated with ESS. LDE was not significantly associated with ESS. Excessive daytime sleepiness in patients with mid-stage PD may be more strongly related to anxiety than to other neuropsychologic dysfunction or dopaminergic dosing levels.

Keywords: Excessive daytime sleepiness; Parkinson's disease; Neuropsychology; Mood; Executive functions; Dopamine agonists

1. Introduction

Sleep problems occur in up to 74–98% of patients with Parkinson's disease (PD) [1–3]. They are, in fact, more frequent than previously suspected and are under-diagnosed and under-treated. When present, furthermore, sleep problems of PD significantly increase disability and caregiver burden [1,4–9].

One of the most common sleep problems associated with PD is excessive daytime sleepiness or EDS. Surveys find that between 30 and 75% of patients with PD report significant EDS depending on the definition of EDS used in the study [10–14].

While poor night-time sleep due to motor complications of the disease likely contributes to EDS in PD patients, disease severity alone does not consistently predict complaints of daytime sleepiness [14–17]. Instead, attention has turned to the role of potential neuropsychologic, neuropsychiatric and medication-related factors in accounting for EDS in PD patients.

Medication type and dosage has received the most attention. Frucht et al. [18] reported that use of the newer non-ergot dopamine agonists (i.e. pramipexole and ropinirole), was associated with sudden and irresistible 'sleep attacks' during the day in some PD patients. Since many PD patients drive automobiles, Frucht's findings raised concerns that medication-induced sleep attacks may contribute to automobile accidents involving sleepy PD patients.

Razmy et al. [19], using the Multiple Sleep Latency Test (MSLT) to objectively measure EDS, reported that patients treated with the newer non-ergot agonists did not differ from patients treated with the older ergotiline (bromocriptine or pergolide) agonists with respect to mean MSLT scores. The best predictor of pathologic daytime sleepiness was high levodopa or dopaminergic dose equivalents (LDE).

Other investigators have also reported that they found no special effects of the newer non-ergot agonists on EDS [12,14,15,20]. Nor has high dosing level of dopaminergic medications or measures of levodopa dose equivalent (LDE) reliably predicted EDS. In those papers that have reported correlations between LDE and EDS [15,20], the strength of the correlations did not exceed $r = .30$, Brodsky et al. [14], on the other hand,

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found that mean LDE significantly predicted self-reported 'sleep episodes' while driving.

While the status of the relationship of medication dosing regimes to EDS in PD remains unclear, other potential correlates of EDS in PD patients have begun to receive attention. Gjerstad, Aarsland and Larsen [13] recently reported that EDS was associated with onset of intellectual dysfunction and dementia. Tandberg et al. in a community-based study [11] found that PD patients with EDS had higher Hoehn-Yahr stages, lower scores on cognitive function (MMSE), higher scores for depressive symptoms (on Montgomery and Aasberg Depression Rating Scale or MADRS), and higher frequency of hallucinations than PD patients without EDS. It has also been a robust finding that sleep disturbances in PD are often associated with psychiatric symptomology such as depression, anxiety and hallucinations [21,22].

Despite the documented associations of both cognitive and mood dysfunction with sleep disturbances in PD, neither mood nor cognitive disturbances have yet been adequately assessed for their contributions to EDS in PD. Previous studies of potential neuropsychiatric correlates of EDS in PD have focused almost exclusively on depression and sleepiness. Neither anxiety nor stress has been formally studied as potential contributors to EDS in PD. While a number of groups (e.g. [21,22]) have reported significant correlations between sleep disturbance and hallucinatory phenomena, EDS was not a focus of investigation in those studies. By contrast, in the current work we directly measure, with standardized and validated scales, both EDS and several dimensions of mood disturbance (depression, stress and anxiety), along with medication dosing regimes, and we assess the relationships between these variables quantitatively.

2. Method

2.1. Participants

Twenty-two male patients with PD were recruited from the outpatient Movement Disorders Clinic at the VA Boston Healthcare System, Boston, MA, in the following manner. Dr Raymon Durso, director of the clinic, individually evaluated and diagnosed each of the patients attending clinics during the months the study was conducted in early 2004. Diagnosis of PD was made by Dr Durso on the basis of clinical signs of PD including the presence of a therapeutic response to levodopa as well as the United Kingdom Parkinson's disease Society brain bank clinical criteria [23]. If the patient had no history of and showed no clinical signs of dementia or psychiatric disturbance they were invited to participate. Dementia was diagnosed according to DSM-III criteria. Cognitive impairment was defined as a Mini Mental State Exam (MMSE) score less than 24. Thus the participants were a convenience sample, consisting of all patients who agreed to participate after Dr Durso explained the study to them.

All patients were right-handed. Ten were at Hoehn-Yahr stage II, eleven at stage III, and one at stage IV [24]. All were on some form of dopaminergic medication and were tested while on medications. Patients with a history of substance abuse or head injury were excluded.

Sixteen healthy control subjects (five female) were also recruited and matched in age to the group of PD patients. Controls were not related to patients.

While the two groups did not differ significantly in terms of age, the age-matched healthy controls reported an average level of education three years greater than the

Table 1
Demographic and neuropsychological variables on PD subjects and controls

Variable	Parkinson's disease			Control			p (Mann–Whitney)
	N	Mean (SE)	Range	N	Mean (SE)	Range	
Age	22	73 (1.5)	54–84	16	70 (1.6)	55–79	0.19
Education	19	13 (0.74)	5–20	16	16 (0.47)	12–18	0.0015*
MMSE	22	28 (0.31)	25–30	16	29 (0.22)	27–30	< 0.0001
Logical memory	22	9 (0.65)	3–16	15	12 (0.94)	5–18	0.015*
Tower of London	21	15 (1.0)	5–26	14	17 (1.3)	7–24	0.25
Stroop interference	21	110 (14)	53–270	16	72 (5.3)	42–120	0.018*
DASS total	21	16 (1.8)	1–33	15	8.7 (2.1)	0–31	0.0072*
DASS anxiety	21	5 (0.65)	1–12	15	1.9 (0.87)	0–13	0.00031*
DASS depression	22	4.8 (0.84)	0–14	15	2 (0.72)	0–10	0.017*
DASS stress	22	5.4 (0.77)	0–12	15	4.9 (0.93)	0–10	0.7
LDE	22	570 (81)	50–1400	–	–	–	–
Epworth sleepiness	22	12 (1.1)	2–19	16	8.1 (0.95)	3–15	0.016*

*$p < 0.05$.

PD group ($p=0.0015$). MMSE score averaged 28 for PD patients and 29 for healthy controls ($p<0.0001$). Demographic characteristics of the two groups are summarized in Table 1.

2.2. Measures

2.2.1. Medication effects

To assess effects of medication type and dose on daytime sleepiness and on cognitive and affective functions we compared different medications directly at dosages of equivalent efficacy. We followed Razmy et al. [19] who used a formula to convert medication dosages to levodopa dosage equivalents (LDE). The only relevant medications taken by patients in our sample were carbidopa/levodopa and pramipexole. Consequently our formula was a simplified version of Razmy's, namely:

$$\text{LDE} = 67 \times (\text{pramipexole dose}) + (\text{regular levodopa dose})$$

2.2.2. Epworth sleepiness scale (ESS)

We used the ESS to assess the propensity to daytime sleepiness. It is a validated, easy to administer self-report questionnaire [25]. It is the sum of eight items that ask for ratings on the tendency to doze in a variety of situations. The ratings are scaled from zero (no chance of dozing) to three (high chance of dozing) for each item. Higher scores indicate greater sleepiness as indicated by a higher likelihood to fall asleep during daytime activities. Healthy subjects typically score in the range of 6–8 points. Johns [25] reported a mean score of 17.5 (3.5) for narcoleptics.

2.2.3. Neuropsychologic measures

We chose tests that are known to be sensitive to detection of neuropsychologic dysfunction in PD.

The *Stroop color-word interference procedure*. In this paper we focus on the score derived from the fourth or 'switching' task. In this task the participant must switch between naming the color of the ink in which a color word is printed and reading the word that is printed. On all trials the ink color is different from the color word that is printed. Susceptibility to cognitive interference is calculated as the total time (s) taken to read through the card.

The *Tower of London* task [26]. We used the total achievement score (TAS) in our analyses. The TAS is a composite score reflecting how many towers were completed correctly within the allotted time, and how many moves each correct tower was completed in. A higher score indicates more correct towers completed in fewer moves.

Logical memory test [27]. We administered a logical memory test adapted from the version presented in the Wechsler Memory Scales—Revised (WMS-R). Participants were read a story and then asked immediately, and again after a delay of 20 min, to recall the story. A participant's score was the number of major elements of the story they recalled at 20 min.

Mood tests. We assessed depression, stress and anxiety with the Depression Anxiety and Stress Scale (DASS) developed by Lovibond and Lovibond [28]. Crawford and Henry [29] and Antony et al. [30] have demonstrated excellent reliability, validity and other psychometric properties for the three subscales of the DASS. The test includes 21 questions, 7 in each of the depression, anxiety and stress subscales. For each of the items on the DASS the patient was asked to "Please read each statement and circle a number 0, 1, 2 or 3 that indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement." The response scale is presented as: 0, did not apply to me at all; 1, applied to me to some degree or some of the time; 2, applied to me to a considerable degree, or a good part of the time; 3, applied to me very much, or most of the time. Included on the depression subscale are items such as, "I felt I had nothing to look forward to" and "I felt I wasn't worth much as a person." On the anxiety subscale were such items as "I felt scared without any good reason" and "I was worried about situations in which I might panic and make a fool of myself." The stress subscale included the items: "I found it difficult to relax" and "I felt that I was rather touchy."

2.3. Statistical analysis

Group differences on all of our major outcome variables were assessed using the Mann Whitney U test, and LDE was assessed for the PD group.

Subsequently the relationships between ESS and the other variables were separately investigated in the PD and control groups by computing Spearman correlations and p-values. In the PD group the association between stage and ESS was assessed by the Mann–Whitney test. Since the one Stage IV patient had an ESS score typical of the Stage III group, these two stages were treated as one for purposes of this contrast. The Benjamini–Hochberg adjustment for multiple hypothesis tests was applied to the 12 tests of association for the PD group [31,32]. All other p values are interpreted descriptively.

Subsequently, multiple regression models were fit with ESS as the outcome variable, to confirm that any statistically significant correlation did not result merely from both variables being associated with a third variable in the current data. Complete data were not available on enough subjects to fit a multiple regression using all measures. Consequently, a model was fit without education, based on complete data for 19 subjects, and another model was fit with education but without Tower of London, using complete data on 18 subjects. Only one DASS scale at a time was included in multiple regression models because of collinearity among the subscales.

For multiple regression, transformations were considered to eliminate instabilities associated with skewed variables.

Consequently the inverse of the Stroop interference score was used rather than the raw score. The raw score measures time to completion of a task and is positively skewed, whereas the inverse score measures speed with which the task is completed and has an approximately normal distribution. Except in the case of the Stroop interference score, transformations made no substantial difference in the results, and the results reported are for models without these transformations.

3. Results

3.1. PD vs. control differences on EDS

Mean score on the Epworth Sleepiness Scale (ESS) was significantly elevated in the PD group relative to the healthy elderly control group (a difference of 3.9, $p=0.016$). Thirteen out of 22 or 59% of the patients reached the pathologic sleepiness criterion of an ESS score greater than 10, and five out of 16 or 31% of the control participants did so. These and all comparisons between PD and controls may be seen in Table 1.

3.2. PD vs. control differences on neuropsychologic function

The two groups differed significantly on Mini Mental State (MMSE), logical memory, and Stroop switching score, but not on the Tower of London total achievement score.

3.3. PD vs. control differences on mood scales

The two groups differed significantly on total score on the Depression Anxiety Stress Scale ($p=0.0072$) and on the anxiety ($p=0.00031$) and depression ($p=0.017$) sub-scales.

3.4. Correlates of daytime sleepiness

In PD patients, no evidence of correlation was found between daytime sleepiness (ESS) and any of the following variables: age, years of education, Mini-Mental State Exam (MMSE), logical memory, Total Achievement Score from the Tower of London test, or Stroop interference score (all $p>0.25$). On the other hand, the Epworth sleepiness score was positively correlated with the total score from Depression Anxiety Stress Scale (Spearman rho $=0.59$; $n=21$, $p=0.0059$). The strength of this correlation appeared to be due largely to the correlation between daytime sleepiness and the anxiety subscale of the DASS, which was 0.69 ($n=21$, $p=0.00066$). The correlations of ESS with the DASS total and DASS anxiety scales are the only correlations that remained significant after adjustment for multiple hypothesis tests. See Table 2 for correlations and associated p values.

Mean ESS for the Stage II and Stage III-IV groups did not differ significantly (mean 11.6, SE 1.6 and mean 12.4, SE 1.5, respectively; $p=0.57$). Mean ESS for females and males did not differ significantly (mean 9.2, SE 2.0 and mean 10.6, SE 0.88; $p=0.54$).

A scatterplot of sleepiness by DASS anxiety may be seen in Fig. 1. An increase on the DASS anxiety score equal to ten percent of the range of the DASS anxiety variable was associated with an increase on the Epworth sleepiness score equal to 7% (SE 1.9%) of the range of that variable. Anxiety scores for patients in the pathological range for sleepiness (ESS >10) range from 3 to 12, whereas for those below the pathological range anxiety ranges from 1 to 6.

Multiple regression models confirmed the status of the DASS scale (total, anxiety and depression, $p=0.013$, 0.028, and 0.039, respectively) as the only statistically significant correlate of daytime sleepiness in PD subjects. Results for the anxiety subscale may be seen in Table 3. Results with the total and depression scales, results from the model

Table 2
Spearman correlations between daytime sleepiness (Epworth sleepiness score) and potential correlates

Variable	Parkinson's disease			Control		
	n	Spearman correlation	p	n	Spearman correlation	p
Age	22	−0.086	0.7	16	−0.25	0.34
Education	19	−0.16	0.52	16	−0.078	0.78
MMSE	22	−0.14	0.53	16	−0.31	0.25
Logical memory	22	0.096	0.67	15	−0.032	0.91
Tower of London	21	0.22	0.33	14	−0.19	0.51
LDE	22	−0.16	0.46	–	–	–
Stroop interference	21	0.26	0.25	16	0.016	0.95
DASS Total	21	0.59	0.0059[a]	15	0.56	0.03*
DASS Anxiety	21	0.69	0.00066[a]	15	0.43	0.11
DASS Depression	22	0.46	0.032*	15	0.11	0.68
DASS Stress	22	0.32	0.14	15	0.59	0.021*

*$p<0.05$.
[a] PD correlations satisfying Bejamini–Hochberg multiple testing criterion.

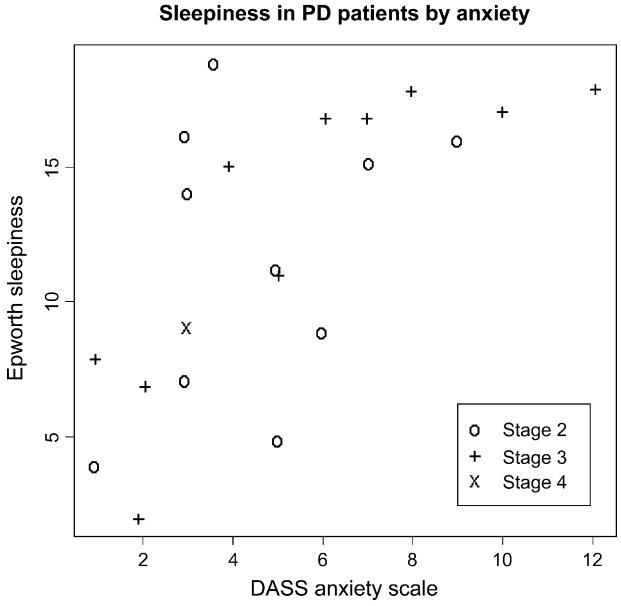

Fig. 1. Epworth sleepiness score by DASS anxiety score for Parkinson's disease patients.

excluding Tower of London but including education, and results using transformed variables were similar.

Among the control subjects, Epworth sleepiness score was positively associated with total DASS ($\rho = 0.56$, $p = 0.03$) and the stress subscale ($\rho = 0.59$, $p = 0.021$). None of these associations remained in the multiple regression models, however (all $p > 0.15$). There was no evidence of a correlation between ESS and anxiety in controls.

With respect to medication effects on daytime sleepiness (ESS), we found no correlation between LDE and Epworth sleepiness score, nor was LDE associated with sleepiness score in any of the multiple regression models studied (Tables 2 and 3).

Table 3
Multiple regression model for Epworth sleepiness score in PD subjects

	Beta	SE	*t*	*p*
Constant	−19	39	−0.48	0.64
H-Y Stage 3–4	1.4	3.4	0.4	0.7
Age	0.037	0.2	0.19	0.86
MMSE	0.86	1.4	0.6	0.56
DASS Anxiety	1.3	0.52	2.6	0.028*
Logical memory	−0.71	0.86	−0.83	0.43
Tower of London	0.33	0.42	0.79	0.45
1/(Stroop interference score)	−37	380	−0.096	0.93
LDE	−0.0012	0.0058	−0.2	0.84

*$p < 0.05$.

4. Discussion

Pathologic daytime sleepiness may put the life of the patient and others in danger (e.g. if the patient drives an automobile when sleepy), and so developing an effective understanding of the underlying causes of EDS is an urgent necessity. We found that patients with Parkinson's disease reported significantly greater levels of excessive daytime sleepiness (EDS) than did age-matched controls and that mood disturbance (specifically increased anxiety) was more strongly related to this EDS than were neuropsychologic dysfunction or dopaminergic dosing level. The relationship is robust, in that it cannot be attributed merely to the fact that many hypotheses were tested.

We found two other studies that examined neuropsychiatric correlates of EDS. Pal et al. studied 40 non-demented patients with PD complaining of some form of sleep disturbance and 23 of their primary caregivers (all were spouses) [16]. They administered the Pittsburgh Sleep Quality Index, Zung's self-rating depression and anxiety scales, Parkinson's Impact Scale (PIMS, only to PD patients), and an additional sleep questionnaire. They found that 57.5% of patients complained of excessive daytime fatigue. Several component sleep scores correlated with anxiety scores, and subjects with global sleep scores greater than or equal to 10 (where 5 meant 'problem sleep') had a higher mean anxiety index. There was no correlation between the degree of sleep dysfunction and the age, severity, duration of PD or its drug treatment.

Tandberg et al. evaluated a community-based sample of 245 patients with PD, obtaining Hoehn-Yahr stage and scores on the UDPRS, MMSE, and the Montgomery and Aasberg Depression Rating Scale (MADRS) [11]. In addition to finding 'markedly and significantly more EDS' in PD patients than in either of two control groups (those with diabetes mellitis and healthy elderly participants), they found MADRS scores of 11.9 (SD 7.4) in PD patients with EDS, substantially more than in patients with no daytime sleepiness (7.3, SD 5.8). Our study extends the results of the Pal and Tandberg studies, giving further evidence of the correlation between daytime sleepiness in Parkinson's disease and neuropsychiatric symptomology, specifically anxiety.

What common pathophysiology might promote both EDS and anxiety in PD patients? We believe reduced striatal and limbic dopaminergic transmission—especially the reduced DA (dopamine) modulation of amygdalar nuclei—may play a crucial role in both [33]. It has long been recognized that administration of dopaminergic agents to patients or animals tends to enhance wakefulness [34,35], thus implying that reducing dopaminergic tone might reduce wakefulness and enhance sleep. These clinical observations have recently been confirmed in experimental animal models. Wisor et al. [34], for example, studied narcoleptic dogs and showed that the anti-narcoleptic compounds modafinil and amphetamine increased

extracellular dopamine and promoted wakefulness. These medications do not affect any other wake-promoting receptors like hypocretin 2. These researchers also studied Dopamine Transporter (DAT) knock-out mice, which suffered from excessive levels of sleepiness and were unresponsive to the normally potent wake-promoting action of modafinil, methamphetamine, and the selective DAT blocker GBR12909. Thus, reduced levels of dopamine transmission appear to be associated with excessive sleepiness. Conversely, normal levels of DA are critical for maintaining wakefulness.

But how might reduced levels of DA promote increased anxiety in the context of sleep? One possibility is that reduced DA transmission in limbic areas releases the amygdala from tonic DA mediated inhibition. Amygdaloid nuclei receive strong inhibitory dopaminergic input from the ventral tegmental area and the dorsal pars compacta of the substantia nigra [36]. Within the amygdala, dopaminergic fibers are most numerous in the central, basal and lateral nuclei—the primary regulatory regions [37]. There are also connections from the amygdala to the ventral striatum which preferentially terminate in the nucleus accumbens [38].

Evidence from many different laboratories and from a variety of animal species indicates that the amygdala specializes in processing of fear, anxiety and attention (see [39] for review of animal studies). The amygdala is one of the most highly activated neural structures during REM sleep [40,41]. We suggest that loss of striatal and limbic dopaminergic transmission, which is part of the pathophysiology of PD [42], results in reduced inhibitory control over the amygdala therefore causing anxiety as well as sleep disturbance. During sleep, PD patients would then be expected to experience signs of disinhibited REM (e.g. vivid dreams, vulnerability to REM behavior disorder etc. [43]) and anxiety. The anxiety would in turn make sleep more difficult and daytime sleepiness more likely.

Interestingly, Albin et al. reported decreased striatal dopaminergic innervation in REM behavior disorder [44]; and Weintraub et al. recently reported that reduced striatal dopamine transporter correlates with anxiety and depression symptoms in Parkinson's disease [45].

Mean Epworth sleepiness scale score for PD patients in this study was 12 (vs. 8.1 for controls). This difference is greater than reported by Högl et al. [12] (PD mean 7.5, SE 4.6 vs. controls mean 5.8, SE 3.0, $p=0.01$); or by Kumar et al. [1] (PD mean 4.9, SD 3.63 vs. controls mean 2.17, SD 2.54, $p<0.05$). The discrepancy may be due to the fact that mean age was higher among the patients we studied than in the Högl et al. and Kumar et al. studies. Studying a larger and more diverse sample than the latter two studies, Brodsky et al. [14] found that the mean ESS scores for PD patients was 9.1 (SE 6.1) vs. 5.7 (SE 4.4) in controls ($p<0.001$). Arnulf et al. [15] studied a group of patients who were referred to a sleep clinic for evaluation of sleep complaints and were similar in age to those of the present study. Mean Epworth Sleepiness score in the Arnulf et al. PD sample was 14.3 (SD 4.1).

We define 'pathologic' daytime sleepiness in our study as a score greater than ten on the Epworth Sleepiness Scale. Fifty-nine percent (13/22) of the PD patients and 31% (5/16) of the controls scored in this pathologic range. In the Högl et al. study [12], 33% of the patients and 11.4% of controls obtained pathologic scores on the ESS. In the Kumar et al. study [10], 21% of PD patients had an ESS score at or above eight on the Epworth as opposed to only 3% of controls ($p<0.05$). In the Brodsky et al. study [14], 40.6% of PD patients compared to 19% of controls scored in the pathologic range ($p<0.01$). Using sleep latency measures Arnulf et al. [15] reported that approximately 40% of PD patients evidence pathologic daytime sleepiness.

It is likely that in addition to amygdaloid disinhibition, there are other causes of EDS in PD. The motor manifestations of PD very likely make it difficult to sleep at night. In addition, neuronal pathology associated with the disease likely contributes to impairment in sleep regulatory processes, both directly via effects on sleep regulatory systems, and indirectly via effects on mood regulation. While the primary pathology of PD involves loss of dopaminergic cells in the substantia nigra (SN) and in the ventral tegmental area or VTA [42], these two subcortical dopaminergic sites give rise to two projection systems important for arousal and mood. The nigrostriatal system, primarily implicated in motor functions, originates in the pars compacta of the SN and terminates in the striatum. The meso-limbic-cortical system, however, contributes to cognitive and affective functioning. It originates in the VTA and terminates in the ventral striatum, limbic sites, amygdala, frontal lobes, and some other basal forebrain areas. Dopamine levels in the ventral striatum, frontal lobes, and hippocampus in patients with PD are approximately 40% of normal [42,46–48]. The degree of nigro-striatal impairment correlates with degree of motor impairment while VTA-mesocortical dopaminergic impairment correlates positively with the degree of intellectual and affective impairment [49–51] in affected individuals.

Although these dopaminergic systems are major contributors to motor, mood and cognitive dysfunction in PD, other forms of PD pathology also likely contribute to sleep disturbances in PD. Lewy body (LB) degeneration and Alzheimer-type changes have been noted in brainstem nuclei implicated in sleep and arousal mechanisms (the noradrenergic locus ceruleus and serotonergic dorsal raphe nucleus), in limbic areas, cerebral cortex and cholinergic forebrain structures [52,53]. The cholinergic pathology in the basal forebrain structures and the LB-type degeneration in brainstem, limbic and in cerebral cortex are likely contributors to both sleep disturbance and intellectual dysfunction.

One limitation of our study was that all patients in this study had similar durations of disease and levels of disease severity (mostly H-Y stage II and III). We also did not have

motor function scores (e.g. Unified Parkinson's disease rating scales) on these patients. We therefore could not directly assess the relationship of disease severity to daytime sleepiness. In other studies, disease severity has not proven to be a reliable correlate of EDS [14–16,20]. Since we excluded any patients with signs of dementia or neuropsychiatric disturbance, the lack of association between our neuropsychologic measures and EDS could be due to the selective inclusion of cognitively intact PD patients.

Another limitation to our study is that we did not include any measures of nighttime insomnia which may influence EDS. As well, the measure we used to assess memory ability (delayed recall condition of the Logical Memory Test) may not be an ideal assessment of memory function in patients with EDS given the attentional lapses associated with EDS. We recommend future studies use alternative techniques to assess memory in these patients such as cued recall techniques (e.g. the Buschke selective reminding test [54]).

In the current work, we have found that PD patients have more daytime sleepiness than age matched healthy controls, and that this excessive daytime sleepiness is related to neuropsychiatric variables (anxiety) but not to dopamine dosing regimen. We propose that a disinhibition of the amygdala system is likely involved in these symptoms resulting from a degeneration of dopaminergic innervation of the limbic system. Since daytime sleepiness is related to increased caregiver burden and likely involved in the increased number of automotive accidents in patients with Parkinson's disease, we must acknowledge the seriousness of this aspect of PD. It is therefore essential that we continue to explore the correlates and causes of sleepiness in PD in order to understand the symptomology better and to develop effective treatments.

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