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GENDER DIFFERENCES IN PARKINSON'S DISEASE: CLINICAL CHARACTERISTICS AND COGNITION

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Abstract

More men than women are diagnosed with Parkinson's disease (PD), and a number of gender differences have been documented in this disorder. Examples of clinical characteristics that appear in men more often than women include rigidity and rapid eye movement behavior disorder, whereas more women than men exhibit dyskinesias and depression. Differences between men and women in cognition have not been extensively examined, though there are reports of deficits in men in aspects of cognition that contribute to activities of daily living, in verbal fluency, and in the recognition of facial emotion, and deficits in women in visuospatial cognition. Side of disease onset may interact with gender to affect cognitive abilities. One possible source of male-female differences in the clinical and cognitive characteristics of PD is the effect of estrogen on dopaminergic neurons and pathways in the brain. This effect is not yet understood, as insight into how the fluctuation of estrogen over the lifetime affects the brain is currently limited. Further attention to this area of research will be important for accurate assessment and better management of PD. Attention should also be directed to multiple covariates that may affect clinical characteristics and cognition. Knowledge about differences in the presentation of PD symptoms in men and women and about the pathophysiology underlying those differences may enhance the accuracy and effectiveness of clinical assessment and treatment of the disease.

Parkinson's disease (PD) is a debilitating neurodegenerative disorder characterized by movement dysfunction and by cognitive and other non-motor impairments. More men than women are diagnosed with PD by a ratio of approximately 2:1 (1-3), and while this ratio suggests the presence of sex and gender differences in PD, the differences between men and women in symptoms, course, and cognitive effects have not been extensively examined. One possible source of differences in cognition, and a growing area of research, is the effect of estrogen on dopaminergic neurons and pathways in the brain. If applied specifically to cognition in PD, research in this area could have a substantial impact on the identification and clinical care of patients with this disorder.

GENDER DIFFERENCES IN CLINICAL SYMPTOM PRESENTATION

Haaxma and colleagues (2007) found specific male-female differences in the presentation of PD (4). The women were on average 2.1 years older than the men at time of diagnosis (53.4 vs 51.3 years) and were more likely to present with tremor as their initial symptom than with bradykinesia or rigidity. Single photon emission computed tomography (SPECT) imaging using the tracer [^{123}I]FR-CIT was used to quantify the amount of nigrostriatal dopamine

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uptake binding. The women had higher levels of striatal uptake binding than the men at time of symptom onset. Based on these findings, the investigators suggested that women have a more benign preclinical phase of PD than men. They proposed a protective role of estrogen because number of children, age at menopause, and duration of fertile life all correlated with later age at onset of PD. Once the disease reached its clinical stage, no male-female differences were seen, meaning that estrogen was important in neuroprotection but offered no benefit once the disease had manifested itself clinically. The implications of the sex difference in striatal binding in PD remain unclear in the literature. Levalaye et al. (2000) (5), Mozley et al. (2001) (6), and Munro et al. (2006) (7) all showed better dopaminergic regulation in the striatum in women than in men, but with varying explanations of mechanisms. Haaxma et al. acknowledged that estrogen level may have served as a proxy for another unknown variable that was actually the critical one in relation to the male-female differences, and gave the example of differential iron levels in men and women.

In a larger-scale study, Scott and colleagues (2000) contrasted symptom characteristics at disease onset and later (8). Relative to onset, at time of second evaluation men listed more symptoms, though women reported that their symptoms caused them more distress (e.g., anxiety and depression) (Table 1). The investigators suggested the reporting differences may have arisen from “differences in social acceptance of communicating emotionality.”

Several studies have assessed activities of daily living (ADLs) along with symptoms of clinical PD presentation. Hariz and colleagues (2003) studied differences between men and women before and after pallidotomy, thalamotomy or deep brain stimulation (9). Women had poorer pre-operative scores on assessments of ADLs, but their post-operative scores were similar to those of the men (Table 1). There were no pre-/post-operative nor male-female differences in overall mental status. Women who had surgery for PD were more impaired and had longer disease duration than men—does this reflect a bias in referral for surgery, or did women cope with their symptoms better and so themselves delayed considering surgery? The larger post-surgical improvement in instrumental ADLs in women than men may have reflected persisting gender roles especially in regard to the ability to engage in domestic tasks, which may have been more important to women than men; further, more men in the sample than women were living with a spouse, suggesting again a possible greater investment in engagement in ADLs for the women.

A study by Accolla and colleagues (2007) evaluated PD patients before and after deep brain stimulation on ADLs and other clinical features of PD (10). Preoperative evaluation showed no differences between men and women for duration or severity of the disease or for tremor, rigidity, or ADLs, but women had more severe dyskinesias and lesser response of bradykinesia to medication. One year post-operatively, bradykinesia was significantly more resistant to treatment in women than in men, the gender difference in dyskinesias was no longer present, and women seemed to show more improvement in ADLs than did men but this result was not significant.

Baba et al. (2005) described ADL levels as well as other clinical characteristics of PD. This group reviewed clinical, historical and demographic characteristics of 1264 individuals (11). Men and women did not differ in regard to average age at onset, duration, rate of progression, or initial symptom. Male-female differences emerged in disease phenotype after onset (Table 1). Because women were more impaired than men in regard to depression level and ADLs, both of which often interact with cognitive abilities, it is possible that women in this sample may have had more cognitive difficulties. These results appear contradictory to those reported by Haaxma and colleagues (4), which described male-female differences at time of disease presentation (e.g., women had later age of onset, initial symptom of tremor). The disparate results may be related to differences in age and disease

duration for the two study samples; participants in the Haaxma study were younger and had shorter disease durations than in the Baba study.

In regard to dyskinesias, several studies have reported greater prevalence in women than men with PD (Table 1), which may be related to levodopa usage. In a study by Zappia and colleagues (2002), women weighed less, took higher doses of levodopa per kilogram of body weight, and had more frequent episodes of dyskinesia than men (12). These results raise the question of current standards of levodopa dosage, as the investigators reported that body weight is generally not taken into consideration in prescribing levodopa dosage, a point also made by Accolla and colleagues (10) in their discussion of why women with PD experience more medication-induced dyskinesia.

Sleep disorders are also common in PD, and gender differences have been found in this area. Two studies examined patients with PD who had rapid eye movement sleep behavior disorder (RBD), in which patients act out violent or dramatic dreams during the REM cycle of sleep. Yoritaka and colleagues (2009) and Ozekmekci and colleagues (2005) found a higher prevalence of RBD in men than women (13,14).

Behavioral problems appear to arise to different extents in men and women with PD, at least in patients with dementia. A large-scale study by Fernandez and colleagues (24,402 PD patients residing in nursing homes) documented that men with PD exhibited more wandering, verbal and physical abusiveness, and inappropriate behavior, whereas women exhibited more depression (15). The investigators made the important observation that there were gender differences in treatment, with men more likely to receive antipsychotic medications and women more likely to receive antidepressants, *regardless of behavioral symptom*.

GENDER DIFFERENCES IN COGNITION

Studies of cognitive changes in PD have focused on patients without dementia and have mainly cited the involvement of the basal ganglia (16-20), prefrontal cortex (21-24), fronto-striatal regions (25-27) or cortico-striatal (frontal and parietal) regions (28-32). Aspects of cognition often associated with these regions in PD include executive function contributing to ADLs, attention, verbal recall, and visuospatial cognition. Cognitive differences between men and women with PD have been largely unexamined. One area of focus has been the comparison in quality of life and ADLs between men and women, functions that require intact cognitive abilities.

Riedel and colleagues (2008) tested 873 PD patients (33). Women were more likely than men to be depressed but there was no mention of using depression as a covariate in analyzing cognitive performance. Participants were assessed with the Mini-Mental State Examination (MMSE) (34), a brief measure of overall mental status; the Clock Drawing Test (CDT), and the Parkinson Neuropsychometric Dementia Assessment (PANDA) (35), a measure including five subscales of cognition commonly affected in PD (word pair associate learning, alternating verbal fluency, visuospatial skills, working memory, and attention). Though there were no differences on the MMSE or PANDA total score, women attained significantly worse scores than men across stages of motor severity. Because the MMSE and PANDA-total were measures of overall cognitive status and the results were not compared to a control group, the investigators were limited in their interpretation of specific cognitive abilities.

Locascio and colleagues (2003), Clark and colleagues (2008), and Davidsdottir and colleagues (2005, 2008) have discussed cognitive impairment in PD more specifically, and reported gender differences. In a rare longitudinal study, Locascio et al. administered tests of

memory, language, visuospatial and frontal-lobe function to healthy adults and PD patients over 10 years (36). Gender differences across groups emerged on the Road Map Test of Direction Sense, a right-left discrimination task that requires egocentric mental rotation in space (men superior) (37), and on a letter fluency test (women superior). In the PD group, men's performance declined faster across disease duration for this test as well as for the other verbal test, category fluency.

Davidssdottir et al. (2005) queried PD patients on visual and spatial symptoms (38). The men and women did not differ in demographic characteristics or in duration of illness. Equal proportions of men and women endorsed at least one problem relating to visual or visuospatial functioning. There was an interaction of side of onset and gender on spatial performance, as men who had left-side onset of PD symptoms (LPD) reported more difficulty in estimating spatial relations than women with LPD; there were no male-female differences for the group who had right-side onset of symptoms (RPD). Side of motor symptom onset is an important consideration in the study of PD, as most patients initially present with symptoms on one side of the body, reflecting the loss of dopamine primarily in the contralateral hemisphere. The right hemisphere is more responsible than the left for many spatial abilities and failure to distinguish patients with LPD from RPD may mean that visuospatial deficits that contribute to functional decline are missed in patients with LPD.

In another study of spatial processing, Clark and colleagues (2008) found that PD patients were deficient in recognition of facial emotion, particularly for the emotions of anger and surprise, and men showed specific deficits in identifying fearful expressions (39). The control group exhibited the opposite pattern: women were less accurate than men at identifying fearful expressions. In this group, women with PD reported more interpersonal problems than control women on a questionnaire assessing difficulties with self-assertion and over-accommodating behavior. These findings are consistent with those of previous studies that found that women with PD reported lower levels of quality of life, another index of social functioning (40), and more depression than men (8,11,15,33). An associated study of visual scanning in a subgroup of the same participants found that control women spent less time fixating on fearful expressions than control men did, but there was no male-female difference in fixation duration for the PD group (41), making the point that for some perceptual or cognitive functions, PD may be associated with the disappearance of normal gender-based differences.

Davidssdottir and colleagues (2008) examined spatial navigation and visuospatial functioning, including measurement of veering during a navigation task, visual ability as assessed through acuity, contrast sensitivity and motion perception, and visuospatial function through tests of line bisection, optic flow perception, egocentric reference, and visual dependence (28). LPD patients were generally more visually dependent than RPD patients, who in turn were more visually dependent than the control group. Gender differences were found in the navigation task, egocentric midline test, line bisection, and motion perception. The results of this study showed that both side of symptom onset and gender were important in understanding visuospatial and visual functioning and navigational veering in patients with PD.

Not all studies of visuospatial function in PD have found male-female differences in performance, including Cronin-Golomb and Braun (1997) (42) on visuospatial problem solving using Raven's Coloured Progressive Matrices, a matching test of visual closure and spatial reasoning (43); Amick and colleagues (2006) on mental rotation (30); and Schendan and colleagues (2009) on hierarchical pattern perception, a test of global and local visual pattern processing (29). The latter two studies reported LPD-RPD effects. Cronin-Golomb (2010) recently reviewed the side of onset literature, describing PD as a disconnection

syndrome (31). Taken together, the several studies suggest that gender differences pertain to some but not all visuospatial abilities, and may interact with side of disease onset. A number of the reported gender differences in clinical characteristics, functional status, and cognition are listed in Table 1.

ROLE OF ESTROGEN

Conflicting results have been found regarding whether or not estrogen has a neuroprotective effect on brain dopaminergic pathways and is involved in the process of PD deterioration and cognitive impairment. Several but not all studies point toward a neuroprotective effect of estrogen on dopamine systems and consequent reduction of risk for PD. The lack of consensus may reflect the fact that the exact mechanisms by which estrogen acts on the dopamine systems are unclear.

A review of the effects of estrogen in the brain was conducted by Liu and Dluzen (2007) (44). The authors found that 24 of 42 animal studies reviewed showed a neuroprotective effect of estrogen against dopamine neurodegeneration in the nigrostriatal regions, five showed a negative effect, and 13 showed no effect. Similarly, of 14 studies of estrogen involvement in human PD patients, seven showed a neuroprotective effect of estrogen whereas four showed anti-dopaminergic and three showed no effect.

The extent to which estrogen is protective against neurodegeneration may be related to the health status of the neurons on which it acts. Chen and colleagues (2006) studied the effect of low and high-dose estradiol on prevention and treatment of neurodegeneration in rat primary hippocampal neurons (45). The therapeutic benefit of estradiol was limited to low-dose estrogen administered before, but not after, induced neurodegeneration. The investigators suggested that as neurodegeneration changes the brain from a healthy to unhealthy state, the effects of estrogen may transition from beneficial to adversarial. If their data were supported by further studies, it would have important implications for clinical decisions regarding estrogen therapy. For further studies in this area, see Brinton et al. (2008) and Liu & Dluzen (2006) (46,47).

Possible neuroprotective effects of estrogen may not be limited to the female brain. A review by Janowsky (2006) suggested that high levels of estrogen may be neuroprotective in men who have low levels of testosterone, but the effects may be more specific to certain cognitive domains (for example, hippocampal-dependent memory) than previously assumed (48). Gillies and McArthur (2010) (49) reviewed the importance of estrogen in relation to neurodegenerative diseases. The authors cited significant organizational and physiological differences between male and female brains that may contribute to differential actions of estrogens in men and women. Understanding such differences may be helpful in explaining the different rates and experiences of PD for men and women as well as pointing toward gender-specific treatments for PD.

The study of the relation of estrogen to PD risk and presentation has several limitations. Often, studies are retrospective and rely solely on either patient recall of relevant medical history or on medical record review. Specific information on disease severity or type is not always collected, and determining age at PD onset is often difficult. Studies do not regularly highlight differences in results between pre- and post-menopausal women. Given these limitations of methodology and interpretability, the existence of conflicting results is understandable. Investigators in this field agree that further study of both endogenous (reproductive hormones over the lifetime) and exogenous (hormone replacement therapy) estrogen levels in PD patients is needed, and that characteristics of estrogen receptors may prove to be important biomarkers of PD (50,51).

CONCLUSIONS

The current state of research on sex and gender effects in PD would benefit from standardization along certain dimensions. It would be useful to see studies that match PD participants (equal numbers of men and women) for key disease-related characteristics, as shown in Table 2 (see also Pavon, Whitson & Okun [2010] for further suggestions) (52). In general, men with PD are more often studied than women, out of proportion to the actual prevalence ratio, and most studies that include both men and women do not examine research data separately for the groups. Gender differences in certain aspects of cognition (e.g., verbal fluency) have been reported, but without a control group, conclusions about whether gender differences in PD are above and beyond gender differences in healthy adults cannot be drawn. It would also be important to match men and women (PD and control) for demographic features such as age and education. Women live longer than men in the general population; the inclusion of age in these analyses will allow us to determine if greater severity of PD symptoms is simply due to the longer survival of women. Groups should also be matched for the presence of premorbid conditions such as depression, anxiety, and sleep disturbances, which are associated with subsequent development of PD.

If matching by groups is not possible, or if the attempt to match would eliminate variables of interest (e.g., the higher prevalence of dyskinesias in women than men with PD), those clinical or demographic dimensions on which groups differ should be included as covariates in analyses of data. For example, if women are more likely to have later disease onset and to have a particular clinical presentation (tremor as initial symptom; presence of dyskinesias), then differences in cognition may be related to one or both of these phenotypes rather than to a gender difference *per se*. Similarly, as depression is known to be associated with cognitive impairment, the higher prevalence of depression in women than men with PD may in itself account for cognitive differences between the groups. A number of the reported gender differences in PD to which analysis of covariates have been applied appear in Table 2.

Detailed and specific cognitive and functional assessment by gender will be important additions to the future literature. In particular, because side and type of symptom onset, along with gender, have been shown to affect some aspects of cognitive performance, these variables should be taken into consideration. Structural and functional imaging studies are lacking in this area and could prove enlightening. Longitudinal prospective studies of sex hormones in men and women would provide more accurate data from which conclusions about their involvement in the development of PD could be drawn. Continued animal research in this area will be vital in directly exploring the effects of hormone manipulation, thereby avoiding the hazards of self-report of hormone levels. Studies in which sex hormone levels are manipulated and brain tissue examined may guide clinical research.

Aside from enhancing our understanding of the phenomenology of PD, research on sex and gender effects is likely to have significant clinical implications. First, medical personnel who recognize that men and women may have different initial presentations of PD may perform more accurate early diagnosis. Second, knowledge of similarities and differences in disease course and response to treatment could affect clinical care. For example, women respond at least as well to surgical treatment of PD as men, but women are older when they undergo surgery. If this age difference arises from a conservative bias of the female PD patient against surgery, then education as to surgery's good potential effects may diminish that bias. If, instead, medical personnel are biased against recommending surgery for women as soon as they do for men, then education should be targeted to those professionals rather than to the patient. As another example, facial masking may violate gender norms for expressivity in women but not in men, and some problems with social relationships in PD

may arise from inaccurate interpersonal impressions of women with more extreme masking (53). Education of PD caregivers and friends may counteract this tendency. A further implication is that women with PD may especially benefit from physical and speech therapy to increase facial and vocal modulation and fluency, in order to mitigate the negative psychosocial effects of facial rigidity (53) and vocal monotony and dysfluency (54).

With these goals and strategies in mind, sex and gender differences in PD may be better delineated than they are at present, and clinical assessment and treatment of the disease may benefit in its accuracy and effectiveness.

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References

1. Bordelon, Y.; Fahn, S. Gender differences in movement disorders.. In: Kaplan, P., editor. Neurologic disease in women. Demos; New York: 2006.
2. Dluzen DE, McDermott JL. Gender differences in neurotoxicity of the nigrostriatal dopaminergic system: implications for Parkinson's disease. *J Gend Specif Med.* 2000; 3(6):36–42. [PubMed: 11253381]
3. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *Am J Epidemiol.* 2003; 157(11):1015–1022. [PubMed: 12777365]
4. Haaxma CA, Bloem BR, Borm GF, et al. Gender differences in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2007; 78(8):819–824. [PubMed: 17098842]
5. Lavalaye J, Booij J, Reneman L, Habraken JB, van Royen EA. Effect of age and gender on dopamine transporter imaging with [123I]FP-CIT SPET in healthy volunteers. *Eur J Nucl Med.* 2000; 27(7):867–869. [PubMed: 10952500]
6. Mozley LH, Gur RC, Mozley PD, Gur RE. Striatal dopamine transporters and cognitive functioning in healthy men and women. *Am J Psychiatry.* 2001; 158(9):1492–1499. [PubMed: 11532737]
7. Munro CA, McCaul ME, Wong DF, et al. Sex differences in striatal dopamine release in healthy adults. *Biol Psychiatry.* 2006; 59(10):966–974. [PubMed: 16616726]
8. Scott B, Borgman A, Engler H, Johnels B, Aquilonius SM. Gender differences in Parkinson's disease symptom profile. *Acta Neurologica Scandinavica.* 2000; 102(1):37–43. [PubMed: 10893061]
9. Hariz GM, Lindberg M, Hariz MI, Bergenheim AT. Gender differences in disability and health-related quality of life in patients with Parkinson's disease treated with stereotactic surgery. *Acta neurologica Scandinavica.* 2003; 108(1):28–37. [PubMed: 12807390]
10. Accolla E, Caputo E, Cogiamanian F, et al. Gender differences in patients with Parkinson's disease treated with subthalamic deep brain stimulation. *Mov Disord.* 2007; 22(8):1150–1156. [PubMed: 17469208]
11. Baba Y, Putzke JD, Whaley NR, Wszolek ZK, Uitti RJ. Gender and the Parkinson's disease phenotype. *Journal of neurology.* 2005; 252(10):1201–1205. [PubMed: 16151602]
12. Zappia M, Crescibene L, Arabia G, et al. Body weight influences pharmacokinetics of levodopa in Parkinson's disease. *Clinical neuropharmacology.* 2002; 25(2):79–82. [PubMed: 11981233]
13. Yoritaka A, Ohizumi H, Tanaka S, Hattori N. Parkinson's disease with and without REM sleep behaviour disorder: are there any clinical differences? *Eur Neurol.* 2009; 61(3):164–170. [PubMed: 19129703]
14. Ozekmekci S, Apaydin H, Kilic E. Clinical features of 35 patients with Parkinson's disease displaying REM behavior disorder. *Clin Neurol Neurosurg.* 2005; 107(4):306–309. [PubMed: 15885389]

15. Fernandez HH, Lapane KL, Ott BR, Friedman JH. Gender differences in the frequency and treatment of behavior problems in Parkinson's disease. SAGE Study Group. Systematic Assessment and Geriatric drug use via Epidemiology. *Mov Disord.* 2000; 15(3):490–496. [PubMed: 10830414]
16. Cropley VL, Fujita M, Bara-Jimenez W, et al. Pre- and post-synaptic dopamine imaging and its relation with frontostriatal cognitive function in Parkinson disease: PET studies with [11C]NNC 112 and [18F]FDOPA. *Psychiatry Res.* 2008; 163(2):171–182. [PubMed: 18504119]
17. Sawamoto N, Honda M, Hanakawa T, et al. Cognitive slowing in Parkinson disease is accompanied by hypofunctioning of the striatum. *Neurology.* 2007; 68(13):1062–1068. [PubMed: 17389313]
18. Sawamoto N, Piccini P, Hotton G, Pavese N, Thielemans K, Brooks DJ. Cognitive deficits and striato-frontal dopamine release in Parkinson's disease. *Brain.* 2008; 131(Pt 5):1294–1302. [PubMed: 18362097]
19. Shin JC, Ivry RB. Spatial and temporal sequence learning in patients with Parkinson's disease or cerebellar lesions. *J Cogn Neurosci.* 2003; 15(8):1232–1243. [PubMed: 14709239]
20. Smith JG, McDowall J. The implicit sequence learning deficit in patients with Parkinson's disease: a matter of impaired sequence integration? *Neuropsychologia.* 2006; 44(2):275–288. [PubMed: 15964035]
21. Cotelli M, Borroni B, Manenti R, et al. Action and object naming in Parkinson's disease without dementia. *Eur J Neurol.* 2007; 14(6):632–637. [PubMed: 17539940]
22. Crevits L, Vandierendonck A, Stuyven E, Verschaete S, Wildenbeest J. Effect of intention and visual fixation disengagement on prosaccades in Parkinson's disease patients. *Neuropsychologia.* 2004; 42(5):624–632. [PubMed: 14725800]
23. Kawai Y, Suenaga M, Takeda A, et al. Cognitive impairments in multiple system atrophy: MSAC vs MSA-P. *Neurology.* 2008; 70(16 Pt 2):1390–1396. [PubMed: 18413566]
24. Rowe JB, Hughes L, Ghosh BC, et al. Parkinson's disease and dopaminergic therapy--differential effects on movement, reward and cognition. *Brain.* 2008; 131(Pt 8):2094–2105. [PubMed: 18577547]
25. Hodgson TL, Tiesman B, Owen AM, Kennard C. Abnormal gaze strategies during problem solving in Parkinson's disease. *Neuropsychologia.* 2002; 40(4):411–422. [PubMed: 11684174]
26. Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *J Neurosci.* 2003; 23(15):6351–6356. [PubMed: 12867520]
27. York MK, Dulay M, Macias A, et al. Cognitive declines following bilateral subthalamic nucleus deep brain stimulation for the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2008; 79(7):789–795. [PubMed: 17965146]
28. Davidsdottir S, Wagenaar R, Young D, Cronin-Golomb A. Impact of optic flow perception and egocentric coordinates on veering in Parkinson's disease. *Brain.* 2008; 131(Pt 11):2882–2893. [PubMed: 18957454]
29. Schendan HE, Amick MM, Cronin-Golomb A. Role of a lateralized parietal-basal ganglia circuit in hierarchical pattern perception: evidence from Parkinson's disease. *Behav Neurosci.* 2009; 123(1):125–136. [PubMed: 19170437]
30. Amick MM, Schendan HE, Ganis G, Cronin-Golomb A. Frontostriatal circuits are necessary for visuomotor transformation: Mental rotation in Parkinson's disease. *Neuropsychologia.* 2006; 44(3):339–349. [PubMed: 16061263]
31. Cronin-Golomb A. Parkinson's disease as a disconnection syndrome. *Neuropsychology Review.* 2010; 20:191–208. [PubMed: 20383586]
32. Nagano-Saito A, Kato T, Arahata Y, et al. Cognitive- and motor-related regions in Parkinson's disease: FDOPA and FDG PET studies. *Neuroimage.* 2004; 22(2):553–561. [PubMed: 15193583]
33. Riedel O, Klotsche J, Spottke A, et al. Cognitive impairment in 873 patients with idiopathic Parkinson's disease. Results from the German Study on Epidemiology of Parkinson's Disease with Dementia (GEPAD). *Journal of Neurology.* 2008; 255(2):255–264. [PubMed: 18204803]

34. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12(3):189–198. [PubMed: 1202204]
35. Kalbe E, Calabrese P, Kohn N, et al. Screening for cognitive deficits in Parkinson's disease with the Parkinson neuropsychometric dementia assessment (PANDA) instrument. *Parkinsonism Relat Disord.* 2008; 14(2):93–101. [PubMed: 17707678]
36. Locascio JJ, Corkin S, Growdon JH. Relation between clinical characteristics of Parkinson's disease and cognitive decline. *Journal of clinical and experimental neuropsychology.* 2003; 25(1): 94–109. [PubMed: 12607175]
37. Money, J. A standardized road map test of direction sense. Academic Therapy Publications; San Rafael, CA: 1976.
38. Davidsdottir S, Cronin-Golomb A, Lee A. Visual and spatial symptoms in Parkinson's disease. *Vision research.* 2005; 45(10):1285–1296. [PubMed: 15733961]
39. Clark US, Nearingard S, Cronin-Golomb A. Specific impairments in the recognition of emotional facial expressions in Parkinson's disease. *Neuropsychologia.* 2008; 46(9):2300–2309. [PubMed: 18485422]
40. Shulman LM. Gender differences in Parkinson's disease. *Gend Med.* 2007; 4(1):8–18. [PubMed: 17584622]
41. Clark US, Nearingard S, Cronin-Golomb A. Visual exploration of emotional facial expressions in Parkinson's disease. *Neuropsychologia.* in press.
42. Cronin-Golomb A, Braun AE. Visuospatial dysfunction and problem solving in Parkinson's disease. *Neuropsychology.* 1997; 11(1):44–52. [PubMed: 9055268]
43. Raven, JC. Guide to using the Coloured Progressive Matrices. H.K. Lewis; London: 1965.
44. Liu B, Dluzen DE. Oestrogen and nigrostriatal dopaminergic neurodegeneration: animal models and clinical reports of Parkinson's disease. *Clinical and experimental pharmacology & physiology.* 2007; 34(7):555–565. [PubMed: 17581209]
45. Chen S, Nilsen J, Brinton RD. Dose and temporal pattern of estrogen exposure determines neuroprotective outcome in hippocampal neurons: therapeutic implications. *Endocrinology.* 2006; 147(11):5303–5313. [PubMed: 16916950]
46. Brinton RD, Thompson RF, Foy MR, et al. Progesterone receptors: form and function in brain. *Front Neuroendocrinol.* 2008; 29(2):313–339. [PubMed: 18374402]
47. Liu B, Dluzen DE. Effect of estrogen upon methamphetamine-induced neurotoxicity within the impaired nigrostriatal dopaminergic system. *Synapse.* 2006; 60(5):354–361. [PubMed: 16838362]
48. Janowsky JS. The role of androgens in cognition and brain aging in men. *Neuroscience.* 2006; 138(3):1015–1020. [PubMed: 16310318]
49. Gillies GE, McArthur S. Estrogen actions in the brain and the basis for differential action in men and women: A case for sex-specific medicines. *Pharmacol. Rev.* 2010; 62(2):155–98. [PubMed: 20392807]
50. Siddle N, Sarrel P, Whitehead M. The effect of hysterectomy on the age at ovarian failure: identification of a subgroup of women with premature loss of ovarian function and literature review. *Fertil Steril.* 1987; 47(1):94–100. [PubMed: 3539646]
51. Brann DW, Dhandapani K, Wakade C, Mahesh VB, Khan MM. Neurotrophic and neuroprotective actions of estrogen: basic mechanisms and clinical implications. *Steroids.* 2007; 72(5):381–405. [PubMed: 17379265]
52. Pavon JM, Whitson HE, Okun MS. Parkinson's disease in women: A call for improved clinical studies and for comparative effectiveness research. *Maturitas.* 65(4):352–358. [PubMed: 20117891]
53. Hemmesch AR, Tickle-Degnen L, Zebrowitz LA. The influence of facial masking and sex on older adults' impressions of individuals with Parkinson's disease. *Psychol Aging.* 2009; 24(3):542–549. [PubMed: 19739910]
54. Jaywant A, Pell MD. Listener impressions of speakers with Parkinson's disease. *J Int Neuropsychol Soc.* 16(1):49–57. [PubMed: 19758475]

Table 1

Gender differences in PD clinical, functional and cognitive symptoms

	Sample size M(F)	Average age	Disease duration	H&Y Score (mean, unless noted)	Men	Women
Accolla et al. (2007)	22 (16)	59.8 (60.1)	14.8 (13.6)	3.3 (3.5) – off meds. 1 (1.3) – on meds		Greater severity of dyskinesias; bradykinesia more resistant to medication or to deep-brain stimulation
Baba et al. (2005)	844 (420)	70.1 (70.6)	7.2 (6.8)	2	More advanced rigidity	More postural instability; greater severity of dyskinesias; more ADL impairment, more likely to be depressed
Clark et al. (2008)	10(10) PD, 11(12) HC	60.2 PD, 59.5 HC	7.3	Median: 2	Deficit in identifying fearful facial expressions	
Davidson et al. (2005)	56 (25)	63.8	7.2	Median: 2	Greater self-perceived disability; more subjective difficulty in initiating movement, more difficulty estimating spatial relations (LPD)	
Davidson et al. (2008)	15 (16) PD, 9 (9) HC	LPD: 60.0, RPD: 62.8, HC: 61.2	5.9	Median: 2		More frequent freezing; greater leftward veering in eyes-closed version of navigation task, leftward bias on line bisection task, more rightward bias on egocentric reference with visual input; worse motion perception
Fernandez et al. (2000)	9,951 (14,101)	Most 75-84	Not reported	Not reported		More likely to be depressed
Haaxma et al. (2007)	156 (97)	53.4(54)	2.5 (2.7)	No direct measurement		More likely to have tremor as initial symptom; older at onset (associated with estrogen status); higher levels of striatal uptake binding at onset
Hariz et al. (2003)	26 (15)	65.7 (65.8)	10.2 (15.1)	3.2 (4.1) – pre-op, 3.1 (3.4) – post-op		Greater severity and duration of dyskinesias; pre-operatively longer PD duration and greater PD severity; more complications to medical treatment, more problems in walking and hygiene; pre- and post-operatively more frequent freezing; more impaired ADLs, greater improvement in ADLs with surgery; lower life satisfaction preoperatively
Locascio et al. (2003)	68 (36)	64.7	5.7	2	Road Map Test: faster decline in scores across disease	

	Sample size M(F)	Average age	Disease duration	H&Y Score (mean, unless noted)	Men	Women
					duration; worse letter fluency performance	
Ozekneki et al. (2005)	54 (16)	67.2 (67.6) – RBD vs. non-RBD	7.5 (5.8) – RBD vs. non-RBD	1.94 (1.73) – RBD vs. non-RBD	Higher prevalence of rapid eye movement sleep behavior disorder	
Riedel et al. (2008)	542 (331)	70.5	6.7	3		Worse scores on the Clock Drawing Test across motor severity stages; more likely to be depressed
Scott et al. (2000)	590 (358)	66+	9.6 (9.3)	Not reported	More problems with vocal pitch, writing, gait, ‘fumblingness’, low power of initiative; more overall symptoms.	More neck pain & lower back pain, more distressed by problems turning in bed, low power of initiative, dry mouth, anxiety at onset; later, more lower back pain; more likely to be depressed.
Shulman (2007)	Review	Review	Review	Review		Lower levels of quality of life
Yoritaka et al. (2009)	70 (80)	68.5	6.4	3	Higher prevalence of rapid eye movement sleep behavior disorder	
Zappia et al. (2002)	91 (73)	66 (64.9)	6.5 (7.6)	2.5 (2.5)		Lower weight, higher levodopa doses; greater frequency dyskinesias

PD = patients with Parkinson's disease; HC = healthy control participants; ADLs = Activities of Daily Living; LPD = PD with left-side symptom onset; RBD = REM sleep behavior disorder

Table 2

Covariates included in analyses for individual studies

	Age at onset	PD duration	Initial symptom	Initial DA level	Control group	PD gender effects from non-PD gender?*	Age (time of study) M vs. F	PD differences due to longevity artifact?
Accolla et al. (2007)	no gender differences	no gender differences	n/a	n/a	no	n/a	no differences	n/a
Baba et al. (2005)	included in analysis	included in analysis	no gender differences	n/a	no	n/a	no differences	n/a
Benedetti et al. (2001)	n/a	n/a	n/a	n/a	yes	n/a	no differences	n/a
Clark et al. (2008)	no gender differences	no gender differences	n/a	n/a	yes	yes	no differences	n/a
Currie et al. (2004)	n/a	n/a	n/a	n/a	yes	n/a	no differences	n/a
Davidson et al. (2005)	included in analysis	no gender differences	n/a	n/a	no	n/a	no differences	n/a
Davidson et al. (2008)	included in analysis	included in analysis	n/a	n/a	yes	yes	no differences	n/a
Fernandez et al. (2008)	n/a	n/a	n/a	n/a	no	n/a	no differences	n/a
Haaxma et al. (2007)	included in analysis	included in analysis (SPECT)	included in analysis (SPECT)	n/a	no	n/a	no differences	n/a
Hartiz et al. (2003)	n/a	included in analysis	n/a	n/a	no	n/a	no differences	Women had longer disease duration
Kenangil et al. (2009)	n/a	n/a	n/a	n/a	yes	n/a	no differences	n/a
Locascio et al. (2003)	included in analysis	included in analysis	n/a	n/a	yes	yes	no differences	n/a
Marder et al. (1998)	n/a	n/a	n/a	n/a	yes	n/a	no differences	n/a
Okun et al. (2004)	n/a	included in analysis	n/a	n/a	yes	n/a	no differences	n/a
Ozekneki et al. (2005)	n/a	n/a	n/a	n/a	no	n/a	no differences	Men had longer disease duration
Popat et al. (2005)	n/a	n/a	n/a	n/a	yes	n/a	no differences	n/a
Ragonese et al. (2004)	n/a	n/a	n/a	n/a	no	n/a	no differences	n/a

	Age at onset	PD duration	Initial symptom	Initial DA level	Control group	PD gender effects different from non-PD gender?*	Age (time of study) M vs. F	PD differences due to longevity artifact?
Ragonese et al. (2006)	included in analysis	n/a	n/a	n/a	no	n/a	no differences	n/a
Riedel et al. (2008)	n/a	n/a	n/a	n/a	no	n/a	no differences	n/a
Rocca et al. (2008)	n/a	n/a	n/a	n/a	yes	n/a	no differences	n/a
Scott et al. (2000)	n/a	no gender differences	n/a	no differences in LD	no	n/a	no differences	n/a
Yoritaka et al. (2009)	n/a	n/a	n/a	n/a	no	n/a	no differences	n/a
Zappia et al. (2002)	no gender differences	no gender differences	n/a	included in analysis	no	n/a	no differences	n/a

PD = Parkinson's disease; DA = dopamine; n/a = not applicable (not mentioned in study); M = male; F = female; HC = healthy control participants; SPECT = single photon emission computed tomography; LD = levodopa.

* See text for description of gender effects for individual studies.