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Review Article

Evidence for Gender Differences in Cognition, Emotion and Quality of Life in Parkinson's Disease?

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ABSTRACT: A number of gender differences have been documented in the incidence and symptomatology of the second most common age-related neurodegenerative disorder, idiopathic Parkinson's disease (PD). Overall, previous reports suggest a less frequent incidence and a more benign phenotype in women mainly in Western populations, which is thought to be mediated by estrogens in particular in early stages of the disease. Not only motor symptoms seem to underlie gender effects, but also non-motor symptoms such as psychiatric and cognitive impairments, which can often precede motor manifestation. However, reliable results for gender differences in PD in particular of cognitive function and emotion processing, having a major impact on quality of life, are lacking. Moreover, studies investigating gender effects in PD in these areas have revealed highly heterogeneous results. The present review summarizes findings of currently available studies on gender effects on neuropsychological tests covering major cognitive domains, emotion processing as well as quality of life in patients with PD. Overall, the occurrence of cognitive impairment in PD seems to be associated with male gender, though inconsistent results were shown in cognitive screening tests. Regarding emotion recognition, men with PD were found to be less accurate than women with PD at identifying fearful expressions, whereas *vice versa* results appeared in healthy subjects. Lower quality of life and greater disability were reported by women compared to men with PD, which corresponds with the results in healthy subjects. Several disease-specific mediators as well as the question of a general gender and age-related effect as observed in healthy individuals are discussed. Increased knowledge on possible gender effects in PD would provide an enhanced insight in underlying pathological mechanisms, and has potential implications for the diagnosis and treatment of PD.

Key words: Parkinson's disease, gender, estrogen, emotion, cognition, quality of life

Parkinson's disease (PD) is the second most frequent age-related neuro-degenerative disorder, characterized by progressive dopaminergic neuron loss in the substantia nigra and formation of Lewy bodies in the central, peripheral and enteric nervous systems [1, 2]. The movement disorder is diagnosed with the onset of the motor symptoms bradykinesia, rigidity, tremor, and/or postural instability. However, a wide spectrum of non-motor symptoms, such as cognitive abnormalities (mild cognitive impairment [MCI] and dementia), psychiatric symptoms, such as depression, anxiety, apathy and sleep disorders, vegetative dysfunctions and sensory symptoms are an integral part of PD [2-4]. Notably, non-motor symptoms can often precede the manifestation of motor

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symptoms by many years and may even dominate the clinical picture in later stages of PD [3].

As shown by a meta-analysis of Taylor, Cook and Counsell [5], the incidence of PD is, with a male:female ratio of 1.46, greater in men than in women of Western populations, though the authors reported a high level of heterogeneity. A large body of research findings suggests that gender may also play a key role in the frequency and severity of symptom presentation in PD [6-14]. Although there are some inconsistent findings, it is assumed that women with PD present with a more benign phenotype than men [9, 15, 16]. Not only that women tend to be older at symptom onset [17], they are also more likely to develop the tremor dominant type, which is in turn associated with a milder motor deterioration than the akinetic-rigid and the equivalent subtype [9, 10, 12]. However, with respect to non-motor symptoms, women present more often with anxiety [18, 19] and depressive symptoms, tend to express higher degrees of complaints [18] and report greater disability and worse quality of life compared to male PD patients [20]. In contrast, motor symptoms like rigidity and gait problems, writing difficulties, speech problems, lack of initiative and inappropriate behavior such as verbal and physical abusiveness, are reported to be more common in men with PD [12, 18, 21, 22].

Moreover, gender differences have been reported in the medical dopaminergic therapy of PD, with women showing less response of bradykinesia to medication [6] and more levodopa induced dyskinesia [16, 18, 19, 21-24]. Apart from this, female PD patients, however, show a greater response to levodopa in general whereas male patients are usually reported to be in need of higher total daily levodopa doses [12, 16]. With respect to neurosurgical treatment – although only a few reports are available – motor impairment improves by stereotactic surgery equally in women and men, though health-related quality of life seems to improve to a greater extent in women [25, 26]. However, larger trials are needed to support this notion.

The causes for gender-related differences in PD are still not fully understood, but it is suggested that they are at least in part a consequence of genetic factors, such as X-linkage of disease [5, 10, 12, 14, 22, 27]. Endocrine-(hormonal) factors may play another essential role [16, 22]. In particular, differential neurobiological effects of estrogens on dopaminergic neurons and cerebral pathways are discussed with both animal and clinical studies suggesting a possible neuro-protective or disease modifying effect of estrogens on dopaminergic neuronal systems [28-30]. Further, epidemiological studies reported variables like parity, age at menopause and fertile life span as influencing factors on the general risk of developing PD as well as the age of disease onset in women [9, 31]. Related to these findings, postmenopausal estrogen therapy is assumed to reduce the general risk of PD and might also present a therapeutic option in manifest PD [31-34]. Regarding the latter, estrogen use was shown to be associated with improvements in motor function [35, 36] and motor fluctuations ("on" and "off" times) [36] in women with PD. Nonetheless, it has to be questioned if estrogen should be considered as a therapeutic option in PD, as some findings showed that postmenopausal intake of estrogens involves increased risk of endometrial abnormalities [37], venous thromboembolic events [38, 39], breast cancer [39, 40], coronary heart disease and stroke [39]. Apart from that, the role of endocrine-(hormonal) factors in PD is still not fully understood. Dopaminergic and non-dopaminergic neuronal degeneration in PD might be multi-factorial [12] and thus, be complemented by geographical factors including environmental, cultural, race/ethnicity and social aspects [6, 41]. Evidence for this is for example emerging from missing gender differences or even a predominance of women with PD in the Asian population [5, 7, 42, 43]. Finally, general gender differences related to the aging brain (e.g. cognitive decline and brain atrophy) might also contribute to the gender differences observed in PD.

In the present review we will focus on gender differences in PD in the context of emotion recognition, cognition and quality of life, which are, as mentioned above, fields of particularly common non-motor conditions in PD [23] with considerable variations in the reported gender aspects. One of the major questions will be, if the encountered differences in women and men with PD are disease-related or rather a matter of a general gender difference also applying to healthy individuals.

Literature Search

Electronic searches for English and German language journal articles were run within the PubMed, Medline and PsycINFO databases in May 2013. The following keywords were used for search: "(Parkinson OR Parkinson's) AND (gender OR sex) AND (emotion/emotional OR cognition/cognitive OR quality of life) NOT (mouse OR rat OR mice)". After deduplication the initial searches identified 406 citations. We only considered those studies which assessed gender or sex differences in emotion, cognition and/or quality of life in idiopathic PD. To identify additional studies that were not retrieved in the initial database searches, we further searched the reference lists of included studies as well as published reviews focusing on similar aspects.

Table 1. Gender differences in cognition in Parkinson's disease

COGNITION						
Characteristics of the study sample						**Gender differences**
Study	Sample Size ♀/♂	Age (years)	Disease duration (years)	UPDRS III / H&Y	Cognitive Examination	
Aarsland et al., 2010 (44)	1346 ♀: 40.2% ♂: 59.8%	67.5	6.1	21.6/ n.a.	- varying assessments across different cohorts (cognitive testing and clinical interviews/ standardized cognitive tests)	Association of MCI with: - male gender, more severe motor symptoms, depression, advanced disease stage, older age at assessment and disease onset
Braak et al., 2005 (57)	88 ♀: 40.9% ♂: 59.1%	♀: 76.2 ± 6.7 ♂: 75.2 ± 6.6	9.5 ± 5.8	n.a. / range: 3-5	- MMSE	Female PD patients: - more frequent cognitive impairment (94,4 %) than men (86,5 %) - lower MMSE test scores
Caranci et al., 2013 (76)	69 ♀: 42.0% ♂: 58.0%	♀: 63.8 ± 9.6 ♂: 65.2 ± 9.1	10.8 ± 7.3	19.7 ± 12.4/ n.a.	- UPDRS I	- Association of plasma alpha-synuclein concentration with cognitive impairment only in men
Folttynie et al., 2005 (77)	291 ♀: 39.5% ♂: 60.5%	65.3	n.a.	24.6/ n.a.	- MMSE - pattern and spatial recognition from CANTAB - tests of verbal fluency - TOL	- Association of low BDNF rates with better performance on TOL in particular in women
Locascio et al., 2003 (69)	104 ♀: 34.6% ♂: 65.4%	64.7 ± 11.4	5.7 ± 5.2	n.a. / range: 1-5	- varying assessments across sessions and subjects (14 tests of memory, language, visuospatial, frontal lobe capacities)	Women overall (across PD and control groups): -worse performance in Money Road Map test - significantly better performance on Fluency for Letters Male PD patients: - worse performance in letter fluency - significantly faster decline in Road Map test - significantly sooner and faster decline on Letter and Category Fluency
Lyons et al., 1998 (16)	630 ♀: 50% ♂: 50%	♀: 71.1 ± 7.6 ♂: 71.1. ± 7.6	♀: 4.6 ± 4.6 ♂: 4.6 ± 4.6	♀: 22.3 ± 11.5/ n.a. ♂: 24.8 ± 12.1/ n.a.	- MMSE	Female PD patients: - higher scores in MMSE (27.6 ± 3.4) relative to men (26.4 ± 4.0)
Nazem et al., 2009 (58)	100 ♀: 30% ♂: 70%	65.3 ± 11.5	7.7 ± 6.4	n.a./ median: 2.0	- MocA - MMSE	Cognitive impairment associated with: - male sex, older age, lower level of education, greater disease severity
Riedel et al., 2008 (23)	873 ♀: 37.9% ♂: 62.1%	70.5 ± 8.6	6.7 ± 5.5	n.a./ 2.7 ± 1.0	- DSM-IV criteria for dementia - MMSE - PANDA (only for a randomly selected subsample) - CDT	Female PD patients: - significantly worse scores on CDT than men - elsewhere gender as an inconsistent contributor

Note: PD = Parkinson's disease, H&Y = Hoehn and Yahr (data are median), UPDRS = Unified Parkinson's Disease Rating Scale (I: Mentation, Behavior and Mood; III: motor score), MCI = Mild cognitive impairment, BDNF = brain-derived neurotrophic factor, MMSE = Mini-Mental-State-Examination, MoCA = Montreal Cognitive Assessment, PANDA = Parkinson Neuropsychometric Dementia Assessment, CANTAB = Cambridge Neuropsychological Test Automated Battery, TOL = Tower of London Test, CDT = Clock Drawing Test; data are given in mean ± standard deviation (unless otherwise indicated), n.a. = not available, ♂ = male, ♀ = female

All in all 18 citations concentrating on gender differences in the specific non-motor symptom areas of cognition, emotion and quality of life qualified for the present review. While eight of these were focussing on gender and cognition and a further nine on gender and quality of life, only one citation could be found for gender and emotion recognition in PD.

Cognition

With about 30% of PD patients suffering from it, cognitive impairment is one of the most important non-motor symptoms in PD [23, 44-50]. It has an enormous impact on the functional outcome of PD with a strong impact on patients' families and caregivers as well [46, 51].

A range of cognitive domains, mainly memory, visual-spatial as well as attention/executive abilities can be affected [45] and both forms, MCI and dementia, are present with a highly neuropsychological and clinical heterogeneity [52]. Additionally, common neuropsychiatric symptoms in PD, such as depression, anxiety, excessive daytime sleepiness, and visual hallucinations, may in turn deteriorate cognitive function [52-55].

The question of gender effects regarding cognitive functioning in PD has been addressed in a few studies, which are summarized in Table 1. A multicenter pooled analysis of 1346 patients with PD from eight different cohorts revealed that MCI in PD was besides older age at assessment, older age at PD onset, depression, more severe motor symptoms and advanced disease stage, associated with male gender [44]. Interestingly, there were differences in the frequency of MCI throughout the eight centers. As the diagnosis of dementia was based on varying assessments across the cohorts, these differences may arise from variances in methodology and sensitivity of individual neuropsychological tests. Nevertheless, after control for center as well as UPDRS motor score, depression and age, gender remained independently correlated with MCI. Similar results were found in another large registry sample of 630 patients, where the most commonly used screening for cognitive deficits, the Mini-Mental State Examination (MMSE) [56], indicated slightly higher scores for women relative to men [16]. However, results must be considered carefully, as authors did not use a multivariate approach or control for confounding variables such as age, motor symptoms or medication. Interestingly in here is also the fact, that Braak, Rub, Jansen Steur, Del Tredici, & de Vos [57], although using the MMSE as well, revealed *vice versa* results, thus lower median test scores for women in a cohort of 88 PD patients (36 women, 52 men) from a single neurologic unit. Even though Braak et al. [57] included a much smaller sample than Lyons et al. [16], they controlled for correlations between MMSE scores and Hoehn & Yahr as well as neuropathologic PD stages. Another aspect to consider at this point is that, whilst the MMSE is used extensively in PD patients, its use in this population has been questioned, especially because it may not be sensitive enough to detect many cases of MCI in PD [23, 58]. The Montreal Cognitive Assessment (MoCA) [59], which is covering the major cognitive domains such as memory, visuospatial and executive function, attention and language functions, has been shown to be more sensitive to detect cognitive impairment in PD [60]. Using this screening instrument, Nazem et al. [58] identified male sex as a possible factor being associated with worse cognitive performance in a sample of 100 PD patients. However, this association appeared only before applying a multivariate model including all other possible mediators (older age, lower formal education and greater disease severity), while afterwards older age remained the only predictor accounting for low MoCA scores. Corresponding with the contradictory results named above, gender was revealed as an inconsistent contributor on cognition in the German study on epidemiology of PD with dementia (GEPAD) [23]. In this study compromising 873 PD patients no gender differences were found in the MMSE and the Parkinson Neuropsychometric Dementia Assessment (PANDA), a screening tool including five cognitive tasks (immediate recall memory, delayed recall memory, alternating verbal fluency, a visuospatial task and a task assessing attention/working memory) and a short depression questionnaire [61]. However, women with PD scored significantly worse than men with PD in the Clock Drawing Test (CDT), a screening instrument for visuo-constructive and executive/spatial abilities [62]. That men excel in spatial tasks, while women perform better on verbal and memory tasks, has been well acknowledged in healthy subjects as well [63-66]. Emphasizing this notion but with the constriction of specialty, cross-sex hormones have been found to increase spatial ability performance but to deteriorate performance on verbal fluency tasks in female to male transsexuals, whereas in contrast, spatial ability decreased and verbal fluency improved after cross-sex hormone treatment in male to female transsexuals [67, 68]. These considerations demonstrate however the importance of a control group to rule out typical gender differences as observed in healthy subjects, when examining gender differences in cognition in PD. Unfortunately none of the studies named above included a control group. As a result, apart from their broad disparity, the reported outcomes are difficult to interpret and it remains unclear weather they are indeed disease-

specific. Capturing this aspect Locascio, Corkin, & Growdon [69] investigated 104 PD patients (68 men, 36 women) and 60 healthy controls (25 men, 35 women) on a variety of cognitive tests. Women, across PD and control subjects, were found to perform worse in the Money Road Map test, a trial requiring egocentric mental rotation in space in a right-left discrimination task [70]. Nonetheless, male PD patients showed a significantly faster decline throughout disease duration than female patients. Women, across PD and control subjects as well, scored higher in the Letter Fluency test, which requires subjects to name as many words as possible beginning with a certain letter in a given time. However, male PD patients declined significantly sooner and faster than female PD patients on the Letter and Category Fluency (requires subjects to name as many words as possible from a certain category in a given time) tests.

Taking together, the literature on gender differences regarding cognitive impairment and dementia in PD is far from clear. Though, the occurrence of cognitive impairment in PD might be associated with male gender, inconsistent results were shown in cognitive screening tests, such as the MMSE. Moreover, it has not been well acknowledged, if these results are disease specific or just a matter of a general gender effect. While women with PD might show up with a slower decline of cognitive functioning compared to men with PD [69], there seems to be evidence for an accelerated age-related cognitive decline in healthy men compared to healthy women as well, as elderly men present an increased decline in performance on attention, verbal memory, spatial memory, and spatial abilities compared to elderly women [64]. This again raises the question of estrogen having a potential neuroprotective effect on cognitive performance. In an observational study of 10145 elderly women with PD, Fernandez and Lapane [71] suggested that estrogen use might moderate the development of cognitive decline in women with PD, as female PD patients being estrogen users were more likely to be cognitively intact as measured by a six-item, seven-level cognitive performance scale (CPS) [72]. This relationship still emerged after adjustment for age, race, and motor impairment in a regression analysis. Corroborating this, estrogen replacement therapy was found to be protective for the development of dementia within the setting of PD and when demented PD patients were compared with controls [73]. In spite of these results, none of the studies on gender differences in cognition in PD named above has considered this aspect as a possible mediator. Studies not only accounting for gender itself but also targeting the effect of hormones on cognitive functioning in PD are needed to establish reliable comparisons between PD patients and healthy controls. Likewise, several more aspects have to be considered when studying gender aspects in cognition in PD: Alpha-synuclein accumulation – intra-cytoplasmic aggregates – is proposed to be the pathological hallmark in PD. As it is suggested that alpha-synuclein passes from the brain to blood [74, 75], plasma alpha-synuclein is proposed as a possible biological marker for PD, although there have been diverging results mainly due to methodological reasons. Interestingly in this context is the fact that in a recent study plasma alpha-synuclein concentration was found to be associated with cognitive impairments, hallucinations, and sleep disorders only in men but not in women with PD [76]. Furthermore, in men, alpha-synuclein concentration was related to disease progression, with lower concentrations in Hoehn and Yahr stage III than in stages I and II and over a period of disease duration of more than ten years.

Another potential marker for PD is the brain-derived neurotrophic factor (BDNF) val66met polymorphism [77]. Etiologically, it is suggested that BDNF has an impact on central dopaminergic synapses and/or the integrity of mesencephalic dopamine neurons. Previous observations in normal individuals and individuals with schizophrenia indicated that BDNF val allele activity predicts better episodic memory performance [78, 79]. Corroborating this with a focus on PD patients, Foltynie et al. [77] revealed that low rates of BDNF secretion were associated with better performance on the Tower of London (TOL) [80] test of planning. This effect was in particular most apparent in women with PD and among patients with prior dopaminergic exposure.

Well gender-balanced studies including control groups without neglecting relevant mediators are needed to answer the question if there is indeed a disease-specific gender effect in cognitive functioning in PD. This could further also provide differential information in underlying pathological mechanisms in the field of cognitive functioning in PD, and maybe even in healthy subjects. Moreover, it could have potential implications for the diagnosis and treatment of MCI and dementia in PD.

Emotion

One of the most basic elements of emotional functioning is the ability to infer other people's emotional states, which is decisive for normal social behavior and interaction. Consequently, deficits in emotion recognition are of upmost clinical significance. Today, impaired facial emotion identification in PD is well acknowledged and has been already investigated in several studies [81-90]. The extent of impaired facial emotion processing appears to be correlated with a variety of interpersonal difficulties, such as complaints of frustration in social relations, feelings of social disconnection, and a desire to connect

with others [81]. Notably, non-verbal emotional information processing and executive function can be disturbed already early in the course of the disease [83]. A meta-analysis of performance on emotion recognition tasks in PD demonstrated a robust link between PD and significant deficits (moderate effect size) in the ability to recognize the emotion portrayed in facial and prosodic stimuli [91]. Hereby, PD patients were more impaired in recognizing negative emotions (anger, disgust, fear, and sadness) than relatively positive emotions (happiness, surprise). The lack of relation to motor impairment underlines the assumption of different underlying pathomechanisms. Of note, depressive symptoms were found to occur independently from emotion recognition deficits. However, the study criteria of the large meta-analysis of performance on emotion recognition tasks in PD including 1295 individuals (594 PD patients) revealed that only 37.5% studies reported matched groups on age, education, and gender composition [91]. While emotion recognition in PD has been now increasingly investigated, most of the studies did not focus on gender issues and/or had small or rather not well gender balanced study groups.

Table 2. Gender differences in emotion in Parkinson's disease

Emotion					
Characteristics of the study sample					Gender differences
Study	Sample Size ♀/♂	Age (years)	Disease duration (years)	UPDRS III / H&Y	
Clark et al., 2008 (81)	20 ♀: 50% ♂: 50%	60.2 ± 8.2	7.3 ± 4.2	n.a. / median: 2.0	Female PD patients: - greater difficulties with self-assertion - more distress related to engaging in overly accommodating behaviors Male PD patients: - specific deficits in the recognition of fearful expressions

Note: H&Y = Hoehn and Yahr (data are median), UPDRS III = Unified Parkinson's Disease Rating Scale (motor score); data are given in mean ± standard deviation (unless otherwise indicated), n.a. = not available, ♂ = male, ♀ = female

To our knowledge, the question of gender effects in the area of facial emotion recognition in PD has been so far examined only by Clark et al. [81; see table 2]. This study on facial emotion recognition in non-demented PD patients revealed that men with PD were significantly less accurate at identifying fearful images than women with PD. Contrarily, women were less accurate than men at identifying fearful expressions in the control group. The authors suggested that male PD patients may experience greater pathology in regions that support the recognition of fearful facial expressions such as the amygdala [92]. Furthermore, the study from Clark et al. [81] also revealed gender differences of interpersonal difficulties in PD. Women with PD reported greater difficulties with self-assertion as well as higher rates of distress related to engaging in overly accommodating behaviors.

Again, additional parameters have to be reflected. As already gender differences were demonstrated in affect and emotion processing in healthy individuals [93, 94], it has to be conjectured if these findings are certainly disease-specific. Healthy women were found to perform better in speeded emotion recognition tasks [95] and in tasks requiring facial expression of emotions than healthy men [96]. Moreover, in a study of facial emotion recognition, sex differences in sensitivity to happy and sad expressions depending on the poser's sex were reported [97]. Women were more sensitive to opposite- than to same-sex expressions, whereas men were differentially poor at detecting sadness in female faces.

Table 3. Gender differences in quality of life in Parkinson's disease

Quality of Life					
Characteristics of the study sample					Gender differences
Study	Sample Size ♀/♂	Age (years)	Disease duration (years)	UPDRS III / H&Y	
Baba et al., 2005 (22)	1264 ♀: 33.2% ♂: 66.8%	♀: 70.6 ±9.1 ♂: 70.1 ±9.5	♀: 6.8 ±6.4 ♂: 7.2 ±6.4	♀: 30.0 ±13.7/ n.a. ♂: 31.0 ±14.2/ n.a.	Female PD patients: - worse ADL capacity - higher proportion of depression
Behari et al., 2005 (113)	278 ♀: 21.6% ♂: 78.4%	♀: 53.1 ± 10.8 ♂: 58.3 ±10.5	♀: 4.4 ± 4.4 ♂: 4.7 ±3.8	n.a.	Female PD patients: - greater reductions in social functioning - worse QOL
Fernandez et al., 2000 (21)	24052 ♀: 58.6% ♂: 41.4%	n.a.	n.a.	n.a.	Female PD patients: - more commonly depressive symptoms Male PD patients: - more commonly wandering, verbal and physical abusiveness, inappropriate behavior
Hariz et al., 2003 (26)	38 ♀: 36.8% ♂:63.2%	♀: 65.8 ±8.1 ♂: 65.7 ±9.0	♀: 15.1 ±5.8 ♂: 10.2 ±5.6	♀: 37.4/ 4.1 ♂: 38.3/ 3.2 (preoperative) ♀: 23.0/ 3.4 ♂: 30.0/ 3.1 (postoperative)	Female PD patients: - greater benefit from surgery than men in ADL, emotions and social life
Hariz et al., 2013 (25)	49 (♀: 36.7% ♂:63.3%)	♀: 57.6 ± 6.6 ♂: 67.7 ±7.8	♀: 12.1 ±5.3 ♂: 12.7 ±6.2	♀: 51.2 ± 10.5/ n.a. ♂: 49.4 ± 16.5/ n.a (pre-operative off-medication) ♀: 16.2 ±10.2/ n.a. ♂: 13.9 ± 7.1/ n.a. (pre-operative on-medication) ♀: 20.0 ± 10.2/ n.a. ♂: 24.8 ± 12.0/ n.a. (post-operative; off-medication on stimulation)	Female PD patients after deep brain stimulation: - greater improvement in ADL (on PDQ-39) - in contrast to men positive effects in fields of mobility, stigma, cognition and summary score of PDQ-39
Hristova et al., 2009 (109)	866 (♀: 47.6% ♂: 52.4%)	♀: 74.0 ± 0.3 ♂: 73.5 ±0.4	6.7 ±0.9	n.a./ range: 1-5	Female PD patients: - significantly worse assessment of QoL in aspects mobility, emotional well-being, social support and bodily discomfort
Kuopio et al., 2000 (114)	228 (out of 282*: ♀: 53.5% ♂: 46.5%)	♀: 73.4 ± 8.4 ♂: 71.3 ±9.5	♀: 9.5 ±5.7 ♂: 8.2 ±5.1	n.a./ 2.6 ± 0.9	Female PD patients: - greater reductions in social functioning
Moore et al., 2005 (111)	124 (♀: 44.4% ♂: 55.6%)	65.8 ±10.2	8.5 ±5.8	48.4 ±17.2./ 2.7 ±0.8	- significant correlation of QoL with disease duration, H&Y staging, disease severity - significantly better QoL of androgynous men and women with PD than other gender groups - significantly better QoL of androgynous PD women than androgynous PD men
Scott et al., 2000 (18)	948 (♀: 37.8% ♂: 62.2%)	n.a. (majority > 66 years)	♀: 9.0 ±5.8 ♂: 9.6 ±6.3	n.a.	Female PD patients: - more frequently neck-pain, low back pain and feeling of distress by their symptoms Male PD patients: - more frequently writing diffculties, fumblingness, gait problems, speech problems, increased flow of saliva, lack of initiative

Note: PD = Parkinson's disease, H&Y = Hoehn and Yahr (data are median), UPDRS III = Unified Parkinson's Disease Rating Scale (motor score), QOL = Quality of life, ADL = Activities of daily living, PDQ-39 = The Parkinson's Disease Questionnaire (long form with 39 questions); data are given in mean ±standard deviation (unless otherwise indicated), n.a. = not available, ♂ = male, ♀ = female; *out of the total sample of 282 patients 228 patients completed the SF-36 = health survey (short form with 36 questions)

Regarding emotional experience, women are more prone to clinical depression [98], and mood fluctuations associated with phases of the menstrual cycle have been documented [99, 100]. In relation to these findings, menstrual cycle phase and thus ovarian hormone concentration may relate to performance in emotion recognition tasks as well [101, 102]. Sex differences in aging in general may also interact with these effects, however, to date there are no studies addressing this issue. Though it is recognized that elderly are in better mood than their young counterparts [103], less is known about age effects on emotion processing. The few studies show that elderly reported fewer negative emotional experiences and greater emotional control [104] as well as increased vulnerability to adverse effects of negative emotional states on memory [105] and other cognitive abilities.

Again, there are mild details for gender effects in emotional processing in PD, but further studies are necessary to elucidate this interesting aspect. Interesting in here is also, that interpersonal difficulties are common in PD and, in many cases, even more detrimental to quality of life than physical symptoms [106-108].

Quality of Life

A few studies examined Quality of Life (QoL) in PD, referring to an individuals' total wellbeing including all emotional, social, and physical aspects of the individuals' life, which may be impacted by the disease, and gender or gender identity. The relation of gender as an important factor on QoL in PD was examined repeatedly (see table 3). A study on gender and the PD phenotype revealed that females showed significantly worse activities of daily living (ADL) capacity [22], while ADL refers to daily self-care activities within an individuals place of residence and/ or in outdoor environments reflecting the functional status (abilities and disabilities) of the individual. A chronic neurodegenerative disease such as PD generates reactions to stress and puts the individuals' coping resources to the test. As gender seems to have a vast impact on self-awareness of clinical symptoms and consequently on quality of life, gender symptom profile differences were studied in 948 PD patients using a questionnaire covering the most common PD-related symptoms [18]. In this study, women reported at symptom-onset neck-pain and low back pain more frequently than men. Moreover, a multi-source, cross-linked long-term care database including 400000 PD patients in nursing homes, the Systematic Assessment and Geriatric drug use *via* Epidemiology (SAGE) database, revealed that gender played a crucial role in determining the frequency and treatment of behavioral problems, parameters greatly relevant for quality of life [21]. Whereas wandering, verbal and physical abusiveness and inappropriate behavior tended to be more common in men with PD, depressive symptoms were more common in women with PD. At time of evaluation writing difficulties, fumblingness, gait problems, speech problems, increased flow of saliva and lack of initiative were more frequent among men than women with PD. A majority of women found their symptoms (e.g. depression) constantly distressing. Corroborating this, a study with 866 PD patients revealed that women assessed QoL regarding the aspects of mobility, emotional well-being, social support and bodily discomfort significantly worse than men [109]. In 2003, it was observed that at treatment with stereotactic surgery (pallidotomy, thalamotomy and deep brain stimulation of the thalamus, pallidum or subthalamic nucleus), female PD patients had a significantly longer duration of disease and higher stage on the Hoehn and Yahr scale as well as worse scores on UPDRS parts II (ADL) and IV (complications) than male PD patients [26]. However, following surgery, both men and women with PD showed improvement, but women experienced greater benefit than men in ADL, in emotions, and in social life. The latter results were replicated in 2013, when the authors investigated possible differences between women and men in QoL in forty-nine consecutive patients (18 women) after deep brain stimulation only [25]. Again, women showed greater improvement in ADL than men and moreover, in contrast to men, showed positive effects in the fields of mobility, stigma and cognition as well as on the summary score of the Parkinson's Disease Questionnaire with 39 questions (PDQ-39) addressing aspects of functioning and well-being in PD patients [110].

Apart from that, gender identity might have an effect on quality of life in PD patients as QoL was found to be significantly better in androgynous men and women than in other gender groups with 100 PD patients. Moreover, QoL of androgynous PD women was significantly better than the androgynous PD men group [111].

Considering QoL in elderly subjects in general, there seems to be an overall gender related difference in the experience of QoL with women experiencing disease-related clinical symptoms more heavily than men as well as longer periods of physical and psychological illnesses [112]. Thus, the lower QoL and greater disability cited by women with PD compared to men with PD, corresponds with the results in healthy subjects. Therefore, further studies are needed to answer the question if gender differences in QoL are disease specific or again a matter of a general difference between the sexes.

Conclusion

The literature concerning gender effects on cognition, emotion and quality of life in PD is limited and provides divergent findings. However, there are some details suggesting that women with PD have a more benign disease outcome including the non-motor aspects cognitive functioning and emotion processing, though they report a more severe experience of disease-related clinical symptoms. Nevertheless, the inconsistent findings of gender as a contributing factor to cognition, emotion and quality of life as well as mostly missing data from respective control groups highlight the need for further high quality studies to determine the question of disease-specific gender effects in PD. Especially in the area of emotional processing, our knowledge about gender effects in PD is very sparse. Aside from enhancing our understanding of the phenomenology and pathobiology of PD, this clinical research is likely to have substantial clinical implications. Moreover, neuroimaging studies on gender differences in PD may provide differential information on functional and neuroanatomical aspects in the fields of cognition, emotion and quality of life.

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