Published in final edited form as:

Behav Neurosci. 2013 April ; 127(2): 135–138. doi:10.1037/a0032142.

Emergence of Nonmotor Symptoms as the Focus of Research and Treatment of Parkinson's Disease: Introduction to the Special Section on Nonmotor Dysfunctions in Parkinson's Disease

Alice Cronin-Golomb

Boston University

Abstract

Parkinson's disease (PD) is traditionally characterized by the cardinal motor symptoms of tremor, rigidity, slowness of movement, and impairments of posture, gait, and balance. A relatively new focus of research and treatment is the nonmotor symptoms of the disease, following from recent understanding of the neuropathological stages. Disruptions of arousal, mood, sleep, and autonomic function before the first motor signs of PD implicate the lower brainstem, which is affected before the substantia nigra and dopaminergic system. In later stages of the disease, the pathology extends to the cortex, accompanied by impairments in cognition and perception. The articles in this special section advance our knowledge of the brain bases of the nonmotor symptoms of PD, including disrupted visual perception, impaired cognition across a range of domains, and psychiatric and artistic manifestations. Subtypes under investigation include those described by side of disease onset (left or right body side), predominant cognitive profile, and gender. Taken together, the articles in this special section reflect the field's growing focus on the nonmotor symptoms of PD, their brain bases, and the corresponding potential for their treatment.

Keywords

Parkinson's disease; nonmotor; brainstem; cognition; subtypes

Shaking Palsy (*Paralysis Agitans*): Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured (Parkinson, 2002, p. 223).

This description opens the first chapter of James Parkinson's (1817/2002) classic monograph, "An Essay on the Shaking Palsy." In keeping with his initial description, Parkinson's disease (PD) today is characterized by the cardinal motor symptoms of resting tremor; rigidity; akinesia or bradykinesia (slowness of movement); impairments of posture, gait, and balance; as well as motor abnormalities such as dyskinesias. The diagnosis, according to the widely used U.K. Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes, Daniel, Kilford, & Lees, 1992), requires only the motor symptoms of bradykinesia and muscular rigidity, tremor, or postural instability. Other supportive prospective positive criteria include unilateral onset and persistent asymmetry,

progressive disorder, course of 10+ years, and response to levodopa—all of these linked closely with the motor symptoms.

In a departure from the traditional view, the nonmotor symptoms of PD have been receiving increasing attention in recent years. Examples of these symptoms include disturbances of cognition, sensation and perception, mood, motivation, behavioral inhibition, sleep, and autonomic function. In his essay, Parkinson described certain common nonmotor signs in individual patients, including autonomic and sleep disruption (though he attributed the latter to tremor). The nonmotor symptoms are prevalent: It is rare to find a patient who does not suffer from one or more. They are troublesome: Patients often cite them as more detrimental to quality of life than the motor symptoms (Chaudhuri, Odin, Antonini, & Martinez-Martin, 2011; Sjö Dahl Hammarlund, Hagell, & Nilsson, 2012). They vary tremendously in type and in when they appear during the disease course. Much remains to be learned about the etiology, clinical presentation, course, treatment, and neurological substrates of these dysfunctions, the existence of which belies the traditional view of PD as exclusively a “movement disorder.”

To what should we attribute the rising interest in the nonmotor components of the disease? In many respects, it is unsatisfying to researchers and clinicians to focus on symptoms for which there is no clear mechanism of action. James Parkinson did not know the etiology of any aspect of the disease—he certainly did not mention the substantia nigra or dopamine—but he did offer the following: “Supposed proximate cause: A diseased state of the *medulla spinalis*, in that part which is contained in the canal, formed by the superior cervical vertebrae, and extending, as the disease proceeds, to the *medulla oblongata*” (Parkinson, 2002, p. 230). Dysfunction of the medulla and other lower brainstem areas, such as the locus ceruleus and raphe nuclei, could account for a number of nonmotor symptoms, including changes in arousal, mood, and autonomic function, but Parkinson's implication of the lower brainstem in the development of the disease seems to have fallen by the historical wayside—certainly by the time of the discovery of the death of dopamine-producing neurons in the substantia nigra, and the subsequent success of levodopa as a treatment for the motor symptoms of PD. The clinical and research emphasis on the substantia nigra and dopamine resulted in a decades-long focus of attention on this neurotransmitter in regard to PD etiology and treatment (reviewed in Goetz, 2011). Unfortunately, dopaminergic treatment does not relieve the nonmotor symptoms of the disease, and relatively little progress was made during this period in understanding what causes these symptoms, much less how to treat them. Chaudhuri and colleagues (2011) have memorably referred to the lack of consideration of treatments of nonmotor symptoms as “therapeutic nihilism.”

The past decade, however, has witnessed a refocusing of attention on the lower brainstem and its potential contributions to the nonmotor symptoms of PD. This refocusing has followed from the publication of articles by Braak and colleagues on the neuropathological staging of PD, relating symptoms to synucleinopathy (density of Lewy bodies and Lewy neurites) in various brain regions over the course of the disease. Besides the olfactory bulbs, lower brainstem areas—including the medulla oblongata (as proposed by Parkinson)—appear to be affected first, well before the substantia nigra. As described by Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici (2004, p. 129):

It is important to bear in mind that during the first two stages, the pathology in nonolfactory sites is confined to the medulla oblongata and pontine tegmentum. Thus, the process that ultimately leads to the full clinical picture of PD does not have, as its point of departure, the substantia nigra... On the contrary, the involvement of the substantia nigra presupposes the existence of an obvious pathology in the medulla oblongata. Indeed, were it to become possible to diagnose PD in the presymptomatic stages 1 or 2, and were a causal therapy to become

available, the subsequent neuronal loss in the substantia nigra could be entirely prevented.

There is mounting evidence of disruptions in the domains of arousal, mood, sleep, and autonomic function before the first motor signs of PD, suggesting the existence of a prodromal phase (“presymptomatic,” according to Braak and colleagues; e.g., Chaudhuri et al., 2011; Gaenslen, Swid, Liepelt-Scarfone, Godau, & Berg, 2011; Gaig & Tolosa, 2009; Jacob, Gatto, Thompson, Bordelon, & Ritz, 2010; Postuma et al., 2012). The terms prodromal or presymptomatic refer to symptoms that manifest before the appearance of the motor symptoms that have always defined the disease. In the later stages (Braak stages 5 and 6), the pathology extends to the cortex: “Inclusion bodies appear first in the prefrontal and high-order sensory association areas of the neocortex (stage 5)..., then in the premotor and first-order sensory association areas, and, finally, in some instances, even in the primary fields (stage 6)...” (Braak et al., 2004).

The cortical pathology as evidenced by the presence of the Lewy inclusion bodies and by cortical thinning, such as that reported for orbitofrontal cortex, ventrolateral prefrontal cortex, and occipitoparietal areas—including the unimodal visual cortex (Tinaz, Courtney, & Stern, 2011)—is accompanied by the expected symptoms in cognition and perception, though these seem not to have been noticed by Parkinson himself (“the senses and intellects being uninjured”). For a helpful depiction of the nonmotor symptoms that may be associated with each Braak stage, see the review by Gaenslen and colleagues (2011).

It is reasonable to attribute the fast growth of research on the nonmotor symptoms of PD to the proposed neuropathological etiologies of nonmotor symptoms, together with the inability of current treatments to adequately address these symptoms. Besides being a disease that afflicts a great number of people and attracts clinicians and researchers who specialize in prevention and treatment, PD is also a “problem” that accommodates the interest of a wide range of neuroscientists, from geneticists to psychologists. Additionally, as is true for many brain disorders, studying PD gives us valuable insights into the structure and function of the normal brain (e.g., see Martinu & Monchi, this issue, pp. 222–236, on cerebrobasal ganglia and cerebrocerebellar circuitry). Further, the fact that PD is a heterogeneous disorder in regard to symptomatology (motor and nonmotor) alerts us to the possibility of subtypes. Subtypes that are currently being studied in the field include, among others, those described by side of disease onset or side of current symptom predominance (reviewed in Cronin-Golomb, 2010), type of initial motor symptom (e.g., tremor, rigidity, disturbances of posture and gait), predominant cognitive profile (nondementia or dementia; or frontal-type vs. posterior-type, the latter as discussed by Miller and colleagues, this issue, pp. 175–183), presence or absence of specific genes (e.g., parkin, LRRK2, COMT, MAPT), and gender (reviewed in Miller & Cronin-Golomb, 2010).

The articles included in this special section on PD broadly advance our knowledge of nonmotor systems involved in the disease, including those supporting visual perception, cognition across a range of domains (touching on both mild cognitive impairment and specific cognitive disturbances in nondemented patients), as well as psychiatric and even artistic manifestations. Each of the articles discusses aspects of brain dysfunction relevant to the nonmotor symptom in question, including cortical and subcortical brain regions as well as sensory periphery (e.g., retina). The order of the articles reflects the general topic areas, with adjacent articles speaking to each other on various levels.

There are two articles on *visual perception*. The first, by Bodis-Wollner, Glazman, and Yerram (this issue, pp. 139–150), is a review of aspects of known visual disturbance in PD. We are especially gratified to have Dr. Bodis-Wollner's contribution, as he initiated research on PD vision beginning in the 1970s, being among the first to convincingly show the error

of James Parkinson's statement in his original essay about the “senses ... being uninjured.” Besides describing visual abnormalities, this article raises the question as to what extent retinal dysfunction contributes to visuospatial disturbances in PD. The relation of retinal and cortical deficits to high-order visuospatial function is addressed in the article by Laudate, Neargarder, and Cronin-Golomb (this issue, pp. 151–163), using multiple methods to establish potential sources of hemifield viewing bias in PD (left vs. right disease onset), including analysis of the thickness of the retinal nerve fiber layer with optical coherence tomography (OCT), analysis of retinal function with frequency doubling technology (FDT), and eye tracking.

Next, there are several articles representing research on a wide range of *cognitive* domains, including attention and executive function, social cognition, emotion recognition, and learning and memory. Attentional disturbance is addressed by Smith, Geissler, Schallert, and Lee (this issue, pp. 164–174), specifically the inability in PD to disengage from one activity and attend to another. This group studied rats in the examination of the central amygdala, which receives nigral dopamine input, and provides evidence for its role in the modulation of disengagement behavior. The importance of this article lies in the implication of subcortical (amygdalar) pathology in the development of a deficit in what is usually thought of as a higher-order cognitive function; if amygdalar pathology precedes cortical pathology, then this sort of attentional disturbance may appear in patients well before the later Braak stages of disease. Offering some support for this idea, Miller, Neargarder, Risi, and Cronin-Golomb (this issue, pp. 175–183) report that measures of attention are more sensitive to differences between patients with mild to moderate PD and healthy adults than are neuropsychological tests from most other cognitive domains. This finding is relevant to growing concerns about mild cognitive impairment in PD and the ability to diagnose it early in the disease course. In the realm of social cognition, Anderson, Simpson, Channon, Samuel, and Brown (this issue, pp. 184–192) found disturbances only in PD patients with mild cognitive impairment, whereas those without mild cognitive impairment performed normally. These investigators did, however, note that even the latter type of patient may experience anxiety in social situations, and suggested that this social anxiety could arise from multiple causes, such as from nondopaminergic pathology associated with anxiety or from cognitive biases as often seen in social phobia. The next article, by Buxton, MacDonald, and Tippet (this issue, pp. 193–203), provides an alternative potential basis for social difficulties by describing patients' impairments in recognizing subtle expressions of emotion. In regard to learning and memory, Schendan, Tinaz, Maher, and Stern (this issue, pp. 204–221) used behavioral measures and functional neuroimaging to show changes in frontostriatal and medial temporal-lobe activation patterns associated with reduced spatial sequence learning. Further consideration of motor sequence learning and motor adaptation (the ability to compensate for changing environments) is provided in the review by Martinu and Monchi (this issue, pp. 222–236), in particular in regard to corticobasal ganglia and corticocerebellar circuitry, respectively. These authors raise the question as to whether the corticocerebellar circuit is recruited in PD to compensate for corticobasal ganglia dysfunction or, instead, whether observed changes in cerebellar activity in PD arise from pathophysiological changes resulting from the disease itself. This broad review of motor and nonmotor disturbances incorporates discussions of anatomy, functional circuitry, PD pathology, metabolic and functional changes, and effects of dopaminergic medications and deep brain stimulation as treatments for PD.

The final section is on *psychiatric and artistic* manifestations of PD. Saez-Francas, Hernández-Vara, Roso, Martín, and Brugué (this issue, pp. 237–244) provide a consideration of apathy in PD and the extent of its independence from central fatigue, which is a feeling of constant exhaustion and difficulty in initiating or sustaining voluntary activities. A key to understanding apathy is that it is not a single construct; the domains of

intellectual curiosity and action initiation are related to fatigue, unlike the domains of emotion and self-awareness. The investigators found effects of subtypes, including by side of symptom severity and by gender, calling for more subtype research. On the other end of the initiation spectrum from apathy are impulse control disorders, also referred to as behavioral addictions or impulsive-compulsive behaviors (ICBs). ICBs occur in a subset of PD patients, often in association with treatment with dopamine agonists. Averbek, Djamshidian, O'Sullivan, Housden, Roiser, and Lees (this issue, pp. 245–255) consolidated data from three studies of ICBs and developed a model to account for reward-guided behavior across the various tasks. Specifically, those with ICBs behave as if they are unable to use contextual information to inform future actions. Finally, Inzelberg (this issue, pp. 256–261) provides a provocative review of the postmedication development of artistic creativity in PD. Although this artistic development seems to be dependent on treatment exposure, it is not usually associated with ICBs, indicating that the relation between creative drive and dopamine dysregulation is not straightforward.

In summary, whereas research and clinical work has traditionally focused on the defining motor features of PD, the current movement in the field is toward an inclusive understanding of the nonmotor symptoms. This special section reflects the growing focus on these nonmotor symptoms, their brain bases, and the attendant potential for their treatment.

Acknowledgments

This work was supported by National Institute of Neurological Disorders and Stroke grant R01NS067128.

I thank Mark Blumberg for his encouragement and generous assistance in the development of this special section. Svetlana Efremova for expert and patient editorial support, Laura Pistorino for technical aid, and the American Psychological Association for approving the section. I am grateful to Elisabeth Murray and Neal Swerdlow for their service in reviewing papers from my lab as well as from other labs when potential conflicts of interest arose. To the contributors—authors and reviewers—I extend my most sincere thanks and admiration. It is my hope that this special section will encourage further research on Parkinson's disease, with the goals of enhancing our understanding of the brain and developing effective treatments for all of the symptoms of PD, motor and nonmotor.

References

- Anderson RJ, Simpson AC, Channon S, Samuel M, Brown RG. Social problem solving, social cognition, and mild cognitive impairment in Parkinson's disease. *Behavioral Neuroscience*. 2012 Oct 15. Advance online publication. 10.1037/a0030250
- Averbek BB, Djamshidian A, O'Sullivan SS, Housden CR, Roiser JP, Lees AJ. Uncertainty about mapping future actions into rewards may underlie performance on multiple measures of impulsivity in behavioral addiction: Evidence from Parkinson's disease. *Behavioral Neuroscience*. 2013; 127:245–255. [PubMed: 23565936]
- Bodis-Wollner I, Glazman S, Yerram S. Fovea and foveation in Parkinson's disease. *Behavioral Neuroscience*. 2013; 127:139–150. [PubMed: 23356330]
- Buxton SL, MacDonald L, Tippett LJ. Impaired recognition of prosody and subtle emotional facial expressions in Parkinson's disease. *Behavioral Neuroscience*. 2013; 127:193–203. [PubMed: 23565934]
- Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Research*. 2004; 318:121–134. 10.1007/s00441-004-0956-9 [PubMed: 15338272]
- Chaudhuri KR, Odin P, Antonini A, Martinez-Martin P. Parkinson's disease: The non-motor issues. *Parkinsonism & Related Disorders*. 2011; 17:717–723. 10.1016/j.parkreldis.2011.02.018 [PubMed: 21741874]
- Cronin-Golomb A. Parkinson's disease as a disconnection syndrome. *Neuropsychology Review*. 2010; 20:191–208. 10.1007/s11065-010-9128-8 [PubMed: 20383586]

- Gaenslen A, Swid I, Liepelt-Scarfone I, Godau J, Berg D. The patients' perception of prodromal symptoms before the initial diagnosis of Parkinson's disease. *Movement Disorders*. 2011; 26:653–658.10.1002/mds.23499 [PubMed: 21370256]
- Gaig C, Tolosa E. When does Parkinson's disease begin? *Movement Disorders*. 2009; 24:S656–S664.10.1002/mds.22672 [PubMed: 19877243]
- Goetz CG. The history of Parkinson's disease: Early clinical descriptions and neurological therapies. *Cold Spring Harbor Perspectives in Medicine*. 2011; 1:1–15.10.1101/cshperspect.a008862
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinicopathological study of 100 cases. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1992; 55:181–184.10.1136/jnnp.55.3.181
- Inzelberg R. The awakening of artistic creativity and Parkinson's disease. *Behavioral Neuroscience*. 2013 Jan 14. Advance online publication. 10.1037/a0031052
- Jacob EL, Gatto NM, Thompson A, Bordelon Y, Ritz B. Occurrence of depression and anxiety prior to Parkinson's disease. *Parkinsonism & Related Disorders*. 2010; 16:576–581.10.1016/j.parkreldis.2010.06.014 [PubMed: 20674460]
- Laudate TM, Neargarder S, Cronin-Golomb A. Line bisection in Parkinson's disease: Investigation of contributions of visual field, retinal vision and scanning patterns to visuospatial function. *Behavioral Neuroscience*. 2013; 127:151–163. [PubMed: 23356329]
- Martinu K, Monchi O. Cortico-basal ganglia and cortico-cerebellar circuits in Parkinson's disease: Pathophysiology or compensation? *Behavioral Neuroscience*. 2012 Dec 17. Advance online publication. 10.1037/a0031226
- Miller IN, Cronin-Golomb A. Gender differences in Parkinson's disease: Clinical characteristics and cognition. *Movement Disorders*. 2010; 25:2695–2703.10.1002/mds.23388 [PubMed: 20925068]
- Miller IN, Neargarder S, Risi MM, Cronin-Golomb A. Frontal and posterior subtypes of neuropsychological deficit in Parkinson's disease. *Behavioral Neuroscience*. 2013; 127:175–183. [PubMed: 23398433]
- Parkinson J. An essay on the shaking palsy. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2002; 14:223–236. Originally published as a monograph by Sherwood, Neely, and Jones (London, 1817). [PubMed: 11983801]
- Postuma RB, Aarsland D, Barone P, Burn DJ, Hawkes CH, Oertel W, Ziemssen T. Identifying prodromal Parkinson's disease: Pre-motor disorders in Parkinson's disease. *Movement Disorders*. 2012; 27:617–626.10.1002/mds.24996 [PubMed: 22508280]
- Sáez-Francàs N, Hernández-Vara J, Roso MC, Martín JA, Brugué MC. The association of apathy with central fatigue perception in patients with Parkinson's disease. *Behavioral Neuroscience*. 2013; 127:237–244. [PubMed: 23339489]
- Schendan HE, Tinaz S, Maher SM, Stern CE. Frontostriatal and mediotemporal lobe contributions to implicit higher-order spatial sequence learning declines in aging and Parkinson's disease. *Behavioral Neuroscience*. 2013; 127:204–221. [PubMed: 23565935]
- Sjödahl Hammarlund C, Hagell P, Nilsson MH. Motor and non-motor predictors of illness-related distress in Parkinson's disease. *Parkinsonism & Related Disorders*. 2012; 18:299–302.10.1016/j.parkreldis.2011.10.015 [PubMed: 22100143]
- Smith ES, Geissler SA, Schallert T, Lee HJ. The role of central amygdala dopamine in disengagement behavior. *Behavioral Neuroscience*. 2013; 127:164–174. [PubMed: 23316710]
- Tinaz S, Courtney MG, Stern CE. Focal cortical and subcortical atrophy in early Parkinson's disease. *Movement Disorders*. 2011; 26:436–441.10.1002/mds.23453 [PubMed: 21462259]