Conceptualization of depression in Parkinson's disease

Jeffrey CL Looi[1,2,3]
May Matias[1,2]
Michelle J Ruzich[1,2,4]

[1]Faculty of Medicine and Centre for Mental Health Research, Australian National University (ANU), Canberra, ACT, Australia; [2]Research Centre for the Neurosciences of Ageing (RESCENA), ACT Health, Canberra, ACT, Australia; [3]Laboratory of Neuroimaging, UCLA School of Medicine, Los Angeles, CA, USA; [4]NSW Institute of Psychiatry, Parramatta, NSW, Australia

Aims: To discuss the current methodological and conceptual difficulties inherent in characterizing the emotional manifestations of neurodegenerative disease through critically reviewing depression as a manifestation of idiopathic Parkinson's disease (PD).
Methods: Selective literature review of the neurobiological, psychological, and physical basis of depressive symptoms in PD from 1993–2003, with reference to key earlier articles.
Conclusions: There are difficulties in defining the syndromes of PD itself as well as depression in PD. The use of more conceptually reductionistic definitions of emotion and behavior in comprehensive longitudinal studies of the natural history of PD is recommended.
Keywords: Parkinson's disease, depression, nosology

> *My propositions serve as elucidations in the following way: anyone who understands me eventually recognizes them as nonsensical, when he has used them – as steps – to climb up beyond them. (He must, so to speak, throw away the ladder after he has climbed up it.)*
> WITTGENSTEIN 1974, p 89

Introduction

We wish to explore some of the epistemological and methodological issues regarding the phenomenology, nosology, and ultimately, the investigation of neuropsychiatric disorders. In particular, we will focus on the constraints of applying standardized criteria for depression (WHO 1992; APA 2000), developed for the relatively neurologically healthy, to emotional disorders such as depression in neurodegenerative disease. As a prototypical neuropsychiatric disorder, Parkinson's disease affects cognition, emotion, autonomic, and motor aspects of the nervous system. In this critical review, we seek to focus on the phenomenon of depression in Parkinson's disease, with a view to better appreciating the difficulties that face those seeking to investigate the nature of emotional disorders in neurodegenerative disease. We acknowledge that other syndromes within Parkinson's disease, such as psychosis, may also lend themselves to such exploration, as may other neuropsychiatric disorders such as Alzheimer's disease and vascular dementias. For brevity, and because the arguments may be similarly applied to a lesser or greater degree in these other conditions, we have focused on depression in Parkinson's disease.

Difficulties in characterizing the emotional manifestations of Parkinson's disease

Parkinson's disease is an age-related neurodegenerative disorder characterized by the physical manifestations of resting tremor, rigidity, bradykinesia, and postural instability (Gelb et al 1999; Schrag et al 2002). Despite Parkinson's original observation of preservation of the mental faculties, it is now well recognized that

Correspondence: Jeffrey Looi
RESCENA, OPMHS, Level 1 Lewisham Bldg, Calvary Hospital, PO Box 254, Jamison ACT 2614, Australia
Tel +61 2 6205 1977
Fax +61 2 6205 1533
Email jeffrey.looi@anu.edu.au

there are cognitive and emotional manifestations of the disease (Waters 1998). Depression has been described as the major psychological complication, with a prevalence of 2%–70% in those suffering from PD (Hoogendijk et al 1998; Becker et al 2002). Indeed, when matched for comparable degrees of physical disability with disorders such as osteoarthritis and diabetes, a higher prevalence of depressive disorders were found in the PD group in a large Danish cohort (Murray 1996; Nilsson et al 2001).

However, the characterization of the emotional and cognitive consequences of cerebral neurodegenerative disease remains fraught with misconceptions and uncertainties. Heretofore, the delineation of the psychiatric consequences of neurodegenerative disease has involved surveying patients suffering from neurodegenerative disease with standardized psychiatric diagnostic instruments to characterize psychiatric syndromes described as depression, mania, anxiety, and psychosis. Such an approach has limitations, particularly in Parkinson's disease (PD), due to diagnostic uncertainties in differential diagnosis of idiopathic PD (the major parkinsonian syndrome) from other etiologically distinct parkinsonian syndromes; manifestations of PD which may present as behavioral mimics or phenocopies of depression (Berrios et al 1995) such as apathy; issues of circular/self-referential classification through application of diagnostic criteria for depression in otherwise healthy persons to diagnose depression in PD; and the ongoing debate as to whether a distinct depression in idiopathic PD exists. Indeed, the conceptual challenge of depression in PD has recently been discussed from a semantic and epistemological viewpoint, with reference to the pathophysiology (Leentjens and Verhey 2002). Our focus is somewhat different, and seeks to specifically explore the conceptual and methodological difficulties of defining depression in PD. In particular, we seek to explore how the application of a predetermined psychiatric paradigm of depression traps us in a conceptual oubliette.

Diagnostic uncertainty in parkinsonian syndromes

Parkinsonism itself is a protean entity and aside from idiopathic Parkinson's disease (PD) may result from Parkinson's-plus syndromes such as corticobasal ganglionic degeneration, multiple systems atrophy, progressive supranuclear palsy, or Lewy-Body dementia (Poewe and Wenning 2002). Furthermore, Parkinsonism may be secondary to toxic insults, infections, cervical/cerebral trauma (such as a component of dementia pugilistica), or cerebrovascular disease. Finally, other unrelated movement disorders may masquerade as Parkinson's disease, such as Huntington's disease, Wilson's disease, or familial olivopontocerebellar atrophy.

In addition, a specific etiopathogenesis has not been identified with putative causative factors including genetic factors, toxins, oxidative stress, mitochondrial dysfunction, glutamergic excitotoxicity, glial, neurotrophic, and apoptosis being postulated (Olanow and Tatton 1999).

The relative paucity of in vivo, clinically valid, available, and specific biomarkers for PD renders differential diagnosis difficult, as does the absence of specific clinical features that may differentiate idiopathic PD from other Parkinsonian syndromes (Gelb et al 1999). Idiopathic Parkinson's disease may therefore be misdiagnosed at rates approaching 20%–30% (Poewe and Wenning 2002); and at autopsy, characteristic neuropathological changes are only confirmed in 75% of cases (Gelb et al 1999). Functional neuroimaging techniques such as assessment of striatonigral dopaminergic activity using I^{123} Beta-CIT or I^{123} FP-CIT single photon emission computerized tomography (SPECT), a ligand for the dopamine transporter in the caudate and putamen, have utility in confirming the diagnosis of Parkinson's disease (Duchesne et al 2002; Piccini and Whone 2004). The ratio of caudate to putamen activity shows a 50% reduction of I^{123} Beta-CIT binding in the putamen by disease presentation in PD, with a relatively poorly differentiating relative reduction of binding in the caudate for atypical Parkinsonian syndromes (Brucke et al 1997; Gerschlager et al 2002; Piccini and Whone 2004). Positron emission tomography (PET) has relatively less clinical utility due to the requirement of a cyclotron for generation of the radioisotopes used. Of the PET modalities, ^{18}F-dopa PET has the most utility, demonstrating loss of up to 50% of normal ^{18}F-dopa (a marker of accumulation and metabolism of levodopa) uptake in caudal putamen; however, again differentiation from progressive supranuclear palsy, multiple systems atrophy, or corticobasal degeneration remains problematic (Antinoni et al 1997; Ghaemi et al 2002; Piccini and Whone 2004).

Leentjens and Verhey (2002), assert that Parkinson's disease is a distinct disease entity in contradistinction to psychiatric syndromal diagnosis such as depression. In contrast, we assert that in clinical practice Parkinson's disease is a syndrome rather than a disease, given that we

are unable to ascertain neurobiological data to confirm the diagnosis. This is supported by the relative lack of valid, specific biomarkers such as functional brain neuroimaging and data on misdiagnosis cited above. Furthermore, idiopathic PD is ipso facto of unknown etiopathogenesis, and clinical features do not necessarily correlate with classical neuropathology. We therefore argue that PD and depression both represent syndromal constructions. However, the core syndrome of idiopathic PD is associated with characteristic neuropathological changes postmortem, and there has been speculation on what neurophysiological, neurochemical, and neuroanatomical alterations may serve as the substrate for possible disturbances of cognition and emotion in PD. Here we find ourselves dashed upon the shores of psychiatric syndromal diagnosis, as depression and other psychiatric complications of PD have been heretofore defined using standardized criteria for psychiatric diagnosis designed for neurologically intact and otherwise healthy persons.

Self-referential or circular definitions of depression in PD

In current psychiatric nosology, depression has been defined by operationalized diagnostic criteria formulated by the American Psychiatric Association (DSM-IV) (APA 2000) and the World Health Organization (ICD-10) (WHO 1992) classification of mental disorders. Thus, the diagnosis of major depressive disorder is predicated on the presence of five or more symptoms: low mood, anhedonia, sleep disturbances, weight loss, psychomotor agitation, fatigue, guilt, poor concentration, and suicidal ideation present for more than two weeks (DSM-IV) (APA 2000). This syndromal diagnosis has little reference to putative etiopathogenesis or clinical course apart from a duration specific qualifying period and mandatory exclusion factors (Leentjens and Verhey 2002). The assessment of depression in clinical research has been made by means of structured clinical interviews and/or assessment via depression rating scales based on these criteria.

These extant criteria and methods for assessing depression have been applied for the diagnosis of "depression" in PD, generating an inherent circularity. That is, one can only characterize depression in PD within the confines of the construct of DSM-IV/ICD-10 major depression, thereby precluding us from identifying possibly unique features of the emotional manifestations of PD. Indeed, this type of circularity is not new in the neuropsychiatric literature and has been remarked upon with the definition of vascular cognitive impairment upon a paradigmatic definition derived from Alzheimer's disease (Looi and Sachdev 1999).

Incidence of parkinsonism in persons with depression

Several studies have identified that depression often predates a diagnosis of PD, providing increasing evidence for a common etiology of the two disorders. There have been several studies that have shown depression to be a risk factor for the development of PD (Nilsson et al 2001; Schuurman et al 2002), and several retrospective case control studies showing that PD is preceded by a prodromal phase, characterized by an increased incidence of mood disorders (Gonera et al 1997; Shiba et al 2000). However, the most substantial evidence has come from an epidemiological study, where the lifetime incidence of depressive disorder was calculated for patients, from a general practice based register, until their diagnosis of PD and compared with that of a matched control population from the same register (Leentjens et al 2003). This study found that at the time of their diagnosis of PD, 9.2% of the patients had a history of depression, compared with 4% of the control population. In addition, Nilsson et al (2002), via analysis of a Danish register, found a significant increased risk for hospitalization because of depression in patients with PD compared with subjects with osteoarthritis or diabetes mellitus, providing further support for the hypothesis that depression in patients with PD is a consequence of a shared pathophysiological basis.

Neurobiological basis of cognitive and emotional symptoms behaviorally equivalent to depression in PD

The known neuropathology of PD comprises age-related degeneration of dopaminergic neurons in the substantia nigra pars compacta associated with intracytoplasmic aggregates of alpha-synuclein known as Lewy bodies (Olanow and Tatton 1999). These neurodegenerative changes and Lewy bodies are also found in the locus coeruleus, nucleus basalis of Meynert, hypothalamus, cerebral cortex, brainstem motor nuclei, and autonomic nervous system (Berg et al 1999; Olanow and Tatton 1999). As would be expected from such widespread neuropathology, the PD process may potentially

Table 1 Neurochemical changes in Parkinson's disease (PD)

		Results		
Authors	**Sample characteristics**	**Dopamine**	**Noradrenaline**	**Serotonin**
Engelborgh et al 2003	Comparison of CSF biogenic amines in PD vs aged matched controls PD(n) = 24 Controls (n) = 30	Dopamine metabolite (DOPAC) significantly lower in PD compared with control	No statistically significant change in CSF NA levels between PD and controls	5HT was significantly higher and 5HIAA was significantly lower in PD group with 5HIAA/5HT ratio lower in PD group reflecting decreased 5HT catabolism
Kuhn et al 1996	Comparison of de novo depressed (PDd) and non-depressed (PDn) Parkinson's disease patients PDd (n) = 14 PDn (n) = 12	No significant difference between CSF levels of dopamine and its metabolites between PDd and the PD groups	No significant difference between CSF levels of noradrenaline and its metabolites between the PDd group and PD group	No significant difference of 5HIAA between the PDd group and the PD group
Pacchetti et al 1990	Comparison between depressed and non-depressed PD patients PD (n) = 52, of which 20 are de novo patients			No significant difference in 5HIAA CSF between PDd and PD
Kostic et al 1987				Significantly lower 5H1AA levels in PD and more so in PDd compared with controls
Turkka et al 1987			Levels of CSF NA was not significantly different between PD and aged matched controls	
Mayeux et al 1986	Comparison between depressed and non-depressed PD patients. 10-day dopamine-free period PD (n) = 49			Levels of CSF 5HIAA was lowest in PDd than in PD
Mayeux et al 1984				Data found that CSF 5HIAA content of PDd was lower than PD

Abbreviations: CSF, cerebrospinal fluid; NA noradrenaline.

impact upon a number of structures, circuits, and neurotransmitter function, yielding widespread effects on cognition and emotion.

The role of neurochemical changes in PD in causing depressive symptomatology remains largely speculative. It is important to emphasize that the majority of data pertain to neurochemical and neuropathological changes in Parkinson's disease per se, rather than in depressed Parkinson's disease patients. We have summarized the relevant findings in Tables 1 and 2, with Table 1 describing neurochemical changes and Table 2 describing neuropathological changes (Mann and Yates 1983; Cash et al 1984; Mayeux et al 1984, 1986; Kostic et al 1987; Turkka et al 1987; Chan-Palay and Asan 1989; Pachetti et al 1990; Paulus and Jellinger 1991; Kuhn et al 1996; Bertrand et al 1997; Engelborgh et al 2003). There are conflicting data on the serotonin metabolite 5-hydroxy-indoleacetic acid, with some studies showing decreased levels in depressed PD patients (Mayeux et al 1984, 1986; Kostic et al 1987) and others equally showing no significant differences (Kuhn et al 1996). The evidence for the effects of dopamine and depression has been similarly lacking (Kuhn et al 1996). At best the role of noradrenaline is speculative at present.

Putative neuroanatomical substrates have been based on neuropsychological evidence of frontal system dysfunction (Starkstein and Mayberg 1992; Murray 1996; Schrag et al 2001; Slaughter et al 2001), frontomesial pathology (Starkstein and Petracca 1998), and frontal system hypometabolism on SPECT and PET (Becker et al 2002). Frontal-executive dysfunction is the most common

Table 2 Neuropathological changes in Parkinson's disease (PD)

		Results		
Authors	**Design**	**Substantia nigra**	**Locus coeruleus (LC)**	**Dorsal raphe nucleus (DRN)**
Mann and Yates 1983	PD (n) = 8. PD cases not recruited for depression.		LC degeneration in PD cases. Greater adrenergic cell loss in those with dementia relating to the disease process.	
Cash et al 1984	PD (n) = 20. Thirteen of the PD patients had dementia. Patients not recruited for depression. Unable to establish diagnosis of depression in any of the cases.		Increased adrenergic receptors in the prefrontal cortex of parkinsonian patients. Greater increases in alpha1 adrenergic receptors were noted in PD patients with dementia. Suggestion that the increase in adrenergic receptors is a compensatory mechanism in relation to a drenergic cell loss.	
Chan-Palay et al 1989	PD (n) = 7. Post-mortem study of heterogenous PD group. Chronic elderly PD patients, not specifically recruited for depression. Five of the PD patients had rapidly progressive dementia MMSE 0–5, two of which were atypically depressed and were not L-dopa responsive.		LC neuronal degeneration and cell loss. Decreased LC length. Greater degeneration of LC was noted in the PDd.	
Paulus and Jellinger 1991	Post-mortem studies of elderly PD patients some with comorbid dementia, depression, and psychosis. Diagnosis of depression and psychosis was retrospective based on clinical notes.	PD patients significant cell loss compared with controls.	Reduced cell count in the LC of PD compared with controls. PD (n) = 37 Controls (n) = 12 No difference in LC count and density in between depressed and non-depressed PD.	Reduced cell count in PD compared with controls. PD (n) = 23 Controls (n) = 6 Density of neurons in the DRN in PD depressed was lower. PD (n) = 9 PDd (n) = 12
Bertrand et al 1997	Post-mortem study of 21 PD cases. One case was known to have severe dementia. Cases did not differentiate between depressed and non-depressed patients.		Significant loss of adrenergic neurons in LC. LC neuronal loss increases with disease duration. Significantly decreased LC neurons in the patient with severe dementia.	

Abbreviations: MMSE, Mini-Mental State Examination.

neuropsychological deficit demonstrated in PD (Levy et al 2002; Cummings and Mega 2003) and its occurrence is predictive of dementia (Mahieux et al 1998; Levy et al 2002). The deficits described comprise problems with memory retrieval, word-list generation, organization of complex visual copying, and shifting of cognitive set (Mahieux et al 1998; Cummings and Mega 2003). Dysfunction in these systems could result in symptomatology consistent with depression such as executive dysfunction and impaired concentration. Furthermore, there is emerging evidence that non-verbal emotional information processing is impaired early in PD (Dujardin et al 2004) and that this may contribute

to a presentation consistent with depression. The role of the basal limbic system and associated brainstem nuclei dysfunction in contributing to depressive symptoms remains more speculative at this stage, but potentially could be responsible for deficits in mood, behavior, and sleep (Berg et al 1999; Becker and Berg 2001).

Disruptions of circuit connectivity in the brain have been postulated as a possible mechanism for post-stroke depression, in the absence of clear evidence of neurotransmitter dysfunction (Herrmann et al 1995). The pathways implicated traverse the basal ganglia and involve the intricate white matter loops interconnecting the structures known as the frontosubcortical circuits, with resultant changes in cognition and emotion, and have been implicated in major depression in otherwise healthy persons (Austin et al 2001). In addition, dysfunction in autonomic circuitry, as evinced by orthostasis and postural instability and its association with depression, has been demonstrated (Berrios et al 1995; Schrag et al 2001). Furthermore, disruption of these frontosubcortical circuits results in frontal-executive dysfunction, such as is found in vascular cognitive impairment (Looi and Sachdev 2000) and which has been noted in uncomplicated depression (Austin et al 2001). It is possible, albeit speculative, that remote upstream or downstream effects described as diaschisis may result from neurodegeneration in the basal ganglia and associated circuitry in PD, and thereby, may contribute to local or distant changes in motor, cognitive, and affective functions resembling depression. This would explain the occurrence of frontal-executive dysfunction, associated depressive symptomatology, and anxiety symptoms in PD. It therefore follows that the core neurobiological changes of PD may result in a neurobehavioral syndrome resembling depression (Cummings and Mega 2003).

Manifestations of PD as behavioral mimics or phenocopies of depression

Behavioral manifestations of PD such as agitation, anxiety, anhedonia, apathy, and psychosis may individually or synergistically serve as phenocopies of depression (Berrios et al 1995). Agitation, apathy, and anxiety have been identified as being highly prevalent in epidemiological surveys of persons with PD (Aarsland et al 1999). These behavioral changes may be misidentified as depression due to their resemblance to clinical manifestations of DSM-IV major depression. Apathy refers to reduced interest and participation in normal purposeful behavior, lack of initiative, and indifference with affective blunting (Pluck and Brown 2002). Apathy has now been recognized as a prominent and important manifestation of the emotional consequences of PD, having been demonstrated to be more prevalent in those with PD compared with equally disabled patients with osteoarthritis in the absence of differences in personality traits or cognition (Pluck and Brown 2002). Up to 40% of patients with PD may experience significant anxiety, a higher than expected level for age-matched controls and that this may be clustered into panic disorder, phobias, and generalized anxiety disorder (Starkstein et al 1993; Walsh and Bennett 2001). In particular, generalized anxiety may closely resemble agitated depression via restlessness (which can be interpreted as psychomotor agitation), rumination on trivial concerns, and seeking of reassurance. Furthermore, panic attacks may also mimic agitated depression. Anhedonia itself has been identified as a prominent neuropsychiatric symptom of PD, in the absence of association with mood (Isella et al 2003) and representing a deficit in novelty seeking behavior. Thus, anhedonia may represent part of the core neuropsychiatric disturbance in PD, secondary to deficits in the dopamine reward circuits, and may masquerade as depression (Menza and Mark 1994). In addition, psychosis may also occur frequently in PD and may therefore mimic a psychotic depression.

The diagnostic confusion is further exacerbated by cognitive and physical manifestations of PD which also resemble features of depression, such as impaired concentration, cognitive/psychomotor slowing, brady-kinesia, reduced libido, fatigue, and sleep disturbance (Happe et al 2001; Leentjens and Verhey 2002; Pluck and Brown 2002; Schuurman et al 2002; Lieberman 2003). There may be somatic preoccupations with genuine physical complications such as dizziness, tinnitus, epigastric pain, headaches, bladder, and bowel disturbances (Leentjens and Verhey 2002).

The idea that the physical and behavioral manifestations of PD may resemble depression and is a neurobiological manifestation of the disorder is not new (Cummings and Mega 2003). Indeed, Berrios and colleagues (1995) concluded that anxiety and depression in a proportion of PD patients was a behavioral phenocopy induced by autonomic dysfunction (Lerner and Whitehouse 2002). However, we would broaden this concept to include the range of cognitive, emotional, and physical symptoms of PD that may mimic the depressive syndrome.

A specific syndrome of low mood in PD?

It would seem self-evident that depression could be conceptualized as an understandable reaction to the suffering caused by PD. However, such an approach has been already been identified as being overly simplistic and is contradicted by the lack of association between disease factors and progression with the degree of severity of depression (Starkstein et al 1989; Troster et al 1995; Lerner and Whitehouse 2002).

Much has been written about a distinct syndrome of low mood or depression characteristic to PD, which is somehow distinct from the conventional definition of "idiopathic" (for want of a better term) depression (Cummings and Masterman 1999; Stocchi and Brusa 2000; Myslobodsky et al 2001; Slaughter et al 2001; Yamamoto 2001; Cummings and Mega 2003). This distinction has proved difficult to demonstrate, and we suggest that this is due to a priori application of conventional criteria for depression to the depressive syndrome of PD, thereby constraining the data obtained as opposed to a more descriptive approach such as using an inventory of psychiatric syndromes. Some authors have identified that depressive cognitions are less prevalent in PD than in idiopathic depression (Yamamoto 2001). Others have identified a greater preponderance of somatic symptoms (sleep disturbance, decreased appetite, and anhedonia), dysphoria, suicidal ideation, and a qualitative difference in the nature of the sadness (Slaughter et al 2001). A majority have stated that anxiety symptoms are prominent, there is a lack of mood-congruent psychosis and there are low suicide rates despite a high frequency of suicidal ideation (Cummings and Masterman 1999; Stocchi and Brusa 2000; Myslobodsky et al 2001; Slaughter et al 2001; Yamamoto 2001). Is anxiety being misdiagnosed as depression? Does the lack of suicidal behavior reflect a syndrome of apathy? What are the comorbidity rates of apathy, anxiety, and agitation in PD? Despite these questions, others maintain that there are no characteristic differences between depression in PD and idiopathic depression in older adults (Erdal 2001).

Climbing up the ladder

We would therefore conclude that Parkinson's disease is, in a clinical setting, a syndrome of considerable heterogeneity. Extant psychiatric diagnostic criteria for depression so closely approximate the clinical cognitive, emotional, and physical manifestations of the PD syndrome so as to render the syndromes indistinguishable in part or whole. How are clinicians, especially in primary care, to struggle with the vicissitudes of diagnosis of depression in PD? The putative neurobiological basis of idiopathic PD may be expected to result in emotional consequences consistent with major depression as currently defined. Phenomenological and clinical understanding of the cognitive and emotional consequences of PD, such as depressive symptoms, can best be advanced by careful integrated longitudinal study of the physical, cognitive, and emotional consequences of PD syndromes. Such longitudinal studies should use more conceptually reductionistic diagnostic criteria for emotional consequences such as apathy, specific anxiety syndromes, anhedonia, insomnia, and psychosis as well as the broader construct of "depression" to better characterize these core phenomena without being constrained to an a priori conceptualization of depression. However, it is not entirely pragmatic to eschew the guideposts of description of emotional distress provided by conventional psychiatric nosology, as these provide at least a means of discourse regarding emotional distress and because research to date has utilized such diagnostic criteria to describe these phenomena. Practically, therefore, we suggest inclusion of descriptors of more discrete cognitive and emotional phenomena as well as including classifications according to standardized criteria for depression in longitudinal studies of the natural evolution of Parkinson's disease, a process which has been possible in the analogous investigation of the emotional and cognitive aspects of cerebrovascular disease (Sachdev et al 2004).

We would propose such longitudinal studies of depression in PD should:

1. Examine patients with early-stage PD;
2. Comprehensively characterize their physical, cognitive, and emotional function using measures of motor dysfunction, autonomic function, disability, anxiety, apathy, anhedonia, and cognitive function;
3. In parallel, collect information on depression according DSM-IV/ICD-10 psychiatric classifications;
4. Examine cognitive and emotional processing of anxious and depressive thinking in PD;
5. Utilize structural and functional brain neuroimaging to assist in identifying the neuroanatomical and neurochemical bases of depressive symptoms in PD.

In this way, we may free ourselves from the conceptual oubliette of a predetermined concept of depressive symptomatology in describing the cognitive and emotional manifestations of Parkinson's disease.

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