Chapter 16
Parkinson's Disease

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Abstract Parkinson's disease (PD) is the most common age-related motoric neurodegenerative disease initially described in the 1800's by James Parkinson as the 'Shaking Palsy'. Loss of the neurotransmitter dopamine was recognized as underlying the pathophysiology of the motor dysfunction; subsequently discovery of dopamine replacement therapies brought substantial symptomatic benefit to PD patients. However, these therapies do not fully treat the clinical syndrome nor do they alter the natural history of this disorder motivating clinicians and researchers to further investigate the clinical phenotype, pathophysiology/pathobiology and etiology of this devastating disease. Although the exact cause of sporadic PD remains enigmatic studies of familial and rare toxicant forms of this disorder have laid the foundation for genome wide explorations and environmental studies. The combination of methodical clinical evaluation, systematic pathological studies and detailed genetic analyses have revealed that PD is a multifaceted disorder with a wide-range of clinical symptoms and pathology that include regions outside the dopamine system. One common thread in PD is the presence of intracytoplasmic inclusions that contain the protein, α-synuclein. The presence of toxic aggregated forms of α-synuclein (e.g., amyloid structures) are purported to be a harbinger of subsequent pathology.

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In fact, PD is both a cerebral amyloid disease and the most common synucleinopathy, that is, diseases that display accumulations of α-synuclein. Here we present our current understanding of PD etiology, pathology, clinical symptoms and therapeutic approaches with an emphasis on misfolded α-synuclein.

Keywords Parkinson's disease · α-synuclein · Biomarkers · Clinical symptoms · Treatment · Lewy body · Etiology

Abbreviations

AAV	Adeno-associated viral vectors
Ab	Amyloid beta
AchE-I	Acetylcholinesterase inhibitors
AAAD	Aromatic amino acid decarboxylase
AD	Alzheimer's disease
ANS	Autonomic nervous system
CBD	Corticobasal degeneration
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
CSF	Cerebrospinal fluid
DAT	Dopamine transporter
DBS	Deep brain stimulation
DDC	DOPA decarboxylase
DLBD	Diffuse Lewy body disease
EDS	Excessive daytime sleepiness
ET	Essential tremor
GAD	Glutamic acid decarboxylase
GDNF	Glial-derived neurotrophic factor
GI	Gastrointestinal
GPe	Globus pallidus external
GPi	Globus pallidus internal
GU	Genitourinary
GWA	Genome wide association
H&E	Hematoxylin and eosin
HLA	Human leukocyte antigen
HSF1	Heat shock transcription factor 1
5-HT	5-hydroxytryptamine
H&Y	Hoehn and Yahr
IV	Intravenous
LBD	Lewy body dementia
L-DOPA	Levodopa
MAPT	Microtubule associated protein tau
MCI	Mild cognitive impairment
MPP+	1-methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine
MRI	Magnetic resonance neuroimaging

MSA	Multiple system atrophy
NBIA 1	Neurodegeneration with brain iron accumulation type 1
NMDA	N-methyl-D-aspartate
NMS	Non-motor symptoms
OH	Orthostatic hypotension
PD	Parkinson's disease
PD-D	Parkinson's disease dementia
PDRP	Parkinson's disease-related profile
PET	Positron emission tomography
PGC-1a	Proliferator-activated receptor gamma coactivator 1-alpha
PPAR-g	Peroxisome proliferator-activated receptor-gamma
PPN	Pedunculopontine nucleus
PSP	Progressive supranuclear palsy
PTEN	Phosphatase and tensin homolog
PTX3	Pentraxin 3
QOL	Quality of life
RBD	Rapid eye movement behavior sleep disorder
REM	Rapid eye movement
ROS	Reactive oxygen species
ScFvs	Single chain antibodies
SN	Substantia nigra
SNP	Single nucleotide polymorphism
SNpc	Substantia nigra pars compacta
SNr	Substantia nigra reticulata
SSRI	Selective serotonin reuptake inhibitor
SNRI	Serotonin and norepinephrine reuptake inhibitor
STN	Subthalamic nucleus
SWEDD	Scans without evidence of dopamine denervation
TZD	Thiazolidinediones
UPDRS	Unified Parkinson disease rating scale
ViM	Ventral intermediate nucleus of the thalamus
VMAT2	Vesicular monoamine transporter type 2
VTA	Ventral tegmental area

16.1 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder of aging and the most common movement disorder. Characterized clinically by resting tremor, bradykinesia, rigidity and postural instability, the primary locus of disease is the nigrostriatal pathway comprised of pigmented, dopaminergic neurons within the substantia nigra pars compacta (SNpc) and attendant projections to the putamen. The invariable loss of these SNpc dopamine neurons and consequent development of dystrophic striatal projections are hallmarks of PD. However, patients often suffer

from gastrointestinal, autonomic, and cognitive deficits with accumulating evidence suggesting that pathology is distributed outside the nigrostriatal pathway and occurs many years prior to overt motor symptoms (Braak and Del Tredici 2008). As with other neurodegenerative disorders such as Alzheimer's disease (AD), Huntington's disease and spongiform encephalopathies, PD is characterized by the accumulation of intracellular protein aggregates, Lewy bodies and Lewy neurites, composed primarily of the protein α-synuclein. Thus, PD is classified as the most common synucleinopathy as well as a cerebral amyloid disorder. This disease is also multifaceted with disparate etiologies, a range of clinical symptoms and variations in pathology and therefore, as discussed in the clinical section of this chapter, PD is now more often considered a syndrome. We suggest that placing all PD patients into the umbrella of "pure PD" can lead to some confusion when one interprets and extrapolates data from all PD patients as pure PD rather than various subtypes such as PD with dementia or PD with depression. Advances in biomarker discovery, imaging techniques, comprehensive clinical examinations and neuropathological evaluations will facilitate the development of novel therapeutics for this disorder. The role of α-synuclein aggregates in PD etiology, clinical symptoms and neuropathology will be the primary focus of this chapter.

16.1.1 Socioeconomic Perspective

A number of studies have been undertaken to examine the etiology and epidemiology of PD and Wirdefeldt et al. provide an excellent and extensive review of the literature (Wirdefeldt et al. 2011a). Meta-analyses have estimated the overall incidence of disease between 12–15 (Hirtz et al. 2007) and 16–19 (Twelves et al. 2003) per 100,000 person-years in US and European populations. Incidence of disease is approximately 1.8 times higher in men versus women (1.5–2.0; (Mayeux et al. 1995; Twelves et al. 2003; Van Den Eeden et al. 2003; Hirtz et al. 2007), reviewed in (Wirdefeldt et al. 2011a). Age is the single greatest risk factor for PD with the number of world-wide cases increasing from an estimated 4.1 million (340,000 US cases) in 2005 to nearly 8.7 million (610,000 US cases) by 2030 (Dorsey et al. 2007). The socioeconomic burden of PD is great with estimates of both direct and indirect costs upward of ~$23 billion annually in the US (Huse et al. 2005) ~€14 billion in Europe. Given the oncoming wave of our aging population, as well as the relatively long disease duration and relentlessly progressive nature of this disease, these costs are predicted to increase greatly in the coming years.

16.1.2 Historical Perspective

First described as the "shaking palsy " in 1817 by James Parkinson, little progress was made toward understanding the locus or mechanism of this disorder until the 20th century. Fritz Lewy (a.k.a. "Friedrich Heinrich Lewy") while working in the laboratory

of Alois Alzheimer, first described the hallmark intracellular inclusions characteristic of PD (Rodrigues e Silva et al. 2010). This was followed by Konstantin Tretiakoff's identification of the substantia nigra (SN) as the site of disease, although earlier anecdotal reports demonstrate an understanding that tumors in the SN region could mimic parkinsonism (Lees et al. 2008). Tretiakoff named the eponymous Lewy body inclusions in honor of Lewy's work and a more detailed description of PD pathology by Foix & Nicolesco subsequently identified the specific loss of pigmented, neuromelanin containing neurons in the SN (Gonzalez-Hernandez et al. 2010). Arvid Carlsson and colleagues identified dopamine as a neurotransmitter enriched in the basal ganglia and proposed that PD resulted from dopamine depletion (Carlsson et al. 1957; Bertler and Rosengren 1959). This would be borne out by studies from Oleh Hornykiewicz and others demonstrating that there is a loss of dopamine in PD brains (Ehringer and Hornykiewicz 1998) and that replacement of dopamine, using the blood-brain barrier permeant precursor, levodopa (L-DOPA) alleviated PD symptoms (Birkmayer and Hornykiewicz 1961), which nearly 50 years later is still the pharmacological mainstay for treating this disease. As of yet no treatment is available which alters the natural history of this devastating neurodegenerative disorder.

PD presents as both a familial/genetic disorder and a sporadic/idiopathic disease whose exact etiology is largely not understood. Clinical reports of parkinsonism following exposure to a variety of compounds demonstrated the potential for an environmental component to disease risk, while the identification that mutations in the gene that encodes for α-synuclein (*SCNA*) could cause familial PD (Polymeropoulos et al. 1997) and is a risk factor for sporadic disease (Simon-Sanchez et al. 2009), provided a genetic context for disease. The critical finding that α-synuclein was a key component of the Lewy body (Spillantini et al. 1997) further linked this gene/protein to potential molecular mechanisms of PD. Interestingly, synuclein had been previously identified as the non-amyloid beta (Aβ) component of amyloid pathologies in AD prior to it being linked to PD pathology, suggesting that a common thread may exist between neurodegenerative protein misfolding diseases (Ueda et al. 1993). In the remainder of this chapter we discuss in detail PD etiology, pathological hallmarks, clinical signs and potential therapeutic approaches with an emphasis on the role of protein aggregation specifically as it relates to α-synuclein.

16.2 Etiology

Similar to other neurodegenerative diseases of aging, PD has a complex etiology that has only started to be decoded with the advent of the modern genomics age. Aside from the relatively rare Mendelian monogenetic forms of disease (see below), studies in twins have indicated a broad range of heritability from little genetic contribution to disease (Tanner et al. 1999; Wirdefeldt et al. 2004) to a more substantial heritability estimate of ∼40 % when using a longitudinal study design (Wirdefeldt et al. 2011b) or after excluding subjects with mutations in known susceptibility genes (Hamza and Payami 2010). A recent meta-analysis of five genome wide association (GWA)

studies estimated ~60 % genetic risk, although the authors caution that this may be an overestimate since environmental factors were not considered in the study design (Consortium et al. 2011). The emerging consensus posits PD as a complex disease with multiple genetic and environmental risk factors.

16.2.1 Monogenetic PD

While the complex nature of PD is consistent with both genetic and environmental risk factors, studies in rare kindreds with inherited disease have identified both autosomal dominant and autosomal recessive forms of monogenetic disease. Many excellent reviews provide in-depth explorations of these genes and the potential mechanisms of their actions in PD (e.g., see (Hardy et al. 2006; Martin et al. 2011)). Instead, here we introduce these genes and attempt to link them to potential molecular mechanisms of disease pathogenesis. As an aside, the two genes (*SNCA*, *LRRK2*) that cause autosomal dominant PD, produce classical, later developing disease with α-synuclein staining Lewy pathology, while the autosomal recessive genes (*PARK*, *PINK1*, *DJ1*) tend to cause earlier onset parkinsonism with or without α-synuclein-positive Lewy pathology and generally with a more slowly evolving, more clinically manageable disease. As our collective understanding regarding genetics, pathogenesis and potential molecular pathways of disease has evolved, it is becoming clear that parkinsonism can occur via separate disease entities with variable pathology and disease course, but with common motoric dysfunction and damage to the SN (Litvan et al. 2007a,b).

16.2.1.1 α-Synuclein

A mutation in the gene encoding the protein α-synuclein (*PARK1/4*, *SNCA*) was the first identified for autosomal dominant PD by Polymeropoulos and colleagues in 1997 (Polymeropoulos et al. 1997). Subsequently, triplication (Singleton et al. 2003) and duplication (Chartier-Harlin et al. 2004) at this locus were identified in PD kindreds with earlier disease manifestation in families with the gene triplication. The autosomal dominant nature of mutations to *SNCA*, coupled with the gene-dosage effect seen in duplication/triplication families and the observation that α-synuclein is a key component of Lewy bodies and neurites (Spillantini et al. 1997), suggests a toxic gain-of-function of this protein. α-Synuclein is a 140-amino acid, natively unfolded protein with a propensity to misfold (reviewed in (Surguchov 2008); *see also* Paleologou and El-Agnaf Chapter 6). *In vitro*, α-synuclein can form oligomers and fibrils (Conway et al. 1998; Hashimoto et al. 1998; Conway et al. 2000) that can be stabilized in the presence of dopamine (Conway et al. 2001), which may in part explain the sensitivity of midbrain dopaminergic neurons to α-synuclein toxicity. Considerable effort has been directed at understanding both the normal and abnormal function of this protein. Both *in vitro* and *in vivo* (over-expression and

knock-out models) studies suggest that α-synuclein may be important in aspects of membrane trafficking dynamics, including roles in neurotransmission and synaptic maintenance and as a molecular chaperone (reviewed in Maguire-Zeiss 2008; Surguchov 2008; Martin et al. 2011). Misfolding of the protein, which can be enhanced by a variety of oxidative and inflammatory stressors, leads to toxic intermediates that are proposed to result in alterations in membrane properties, proteasomal degradation and autophagy. The identification of Lewy body-like pathology in graft cells from a subset of PD patients that underwent fetal neuron transplantation (Kordower et al. 2008a,b) and similar reports of neuron-neuron transmission of α-synuclein in rodent models (Desplats et al. 2009; Kordower et al. 2011), coupled with the Braak hypothesis for a caudal-rostral progression of disease (Braak et al. 2002, 2003a,b), have led some investigators to speculate that α-synuclein has "prion-like" properties that can spread throughout a network of neurons (Angot et al. 2010). However, this hypothesis is controversial and further studies are needed. At the very least, these results suggest that the brain milieu in PD is conducive to α-synuclein misfolding and the eventual development of Lewy body pathology.

16.2.1.2 Leucine-Rich Repeat Kinase 2

Mutations in the gene encoding the LRRK2 protein (*PARK8*, *LRRK2*) were first identified in a number of families with autosomal dominant forms of disease (Paisan-Ruiz et al. 2004; Zimprich et al. 2004). Subsequent studies have now identified *LRRK2* to be the most common mutation in both familial and sporadic PD (Berg et al. 2005; Gilks et al. 2005; Goldwurm et al. 2005; Mata et al. 2006; Healy et al. 2008). While a number of mutations have been described, only seven have been linked to disease with the G2019S mutation being the most common (reviewed in Dachsel and Farrer 2010). Individuals with familial *LRRK2* mutations present with typical parkinsonism and often reveal typical Lewy body pathology, although this is not always the case (Khan et al. 2005; Gaig et al. 2007; Healy et al. 2008; Perry et al. 2008; Hasegawa et al. 2009; Poulopoulos et al. 2012). *LRRK2* encodes a 2527-amino acid protein with both kinase and GTPase activity. Little is currently known about the native substrates or normal function of this protein, although studies suggest roles in process outgrowth, synaptic vesicle dynamics and the autophagy/lysosomal pathway (reviewed in (Greggio et al. 2011; Kumar and Cookson 2011)). Postmortem studies have found variable association of LRRK2-immunoreactivity with α-synuclein and Lewy bodies in PD brains (Zhu et al. 2006; Higashi et al. 2007; Alegre-Abarrategui et al. 2008; Perry et al. 2008), which may be related more to methodological differences rather than pathologic importance. It is notable that the loss of protein function alone in three different *LRRK2*$^{-/-}$ mouse lines had no appreciable effect on the nigrostriatal system (Andres-Mateos et al. 2009; Lin et al. 2009; Tong et al. 2010). However, loss of *LRRK2* expression in the kidney in one of the knockout strains led to profound α-synuclein aggregation, oxidative stress, inflammation and cell death (Tong et al. 2010), while accelerated neuropathology was observed by crossing another of the *LRRK2*$^{-/-}$ strains onto a strain overexpressing mutant human

α-synuclein (Lin et al. 2009). Interestingly, while the conventional wisdom suggests that mutations in *LRRK2* cause a toxic gain of kinase function, the finding of a *LRRK2* single-nucleotide polymorphism (SNP) outside of the G2019S mutation in a large meta-analysis of GWA studies led the authors to the interpretation that mutations in LRRK2 may be due to altered protein expression (Consortium et al. 2011), as has been proposed for *SNCA*.

16.2.1.3 Parkin

Mutations in the *parkin* (*PARK2*) locus were originally identified in five Japanese patients with autosomal recessive juvenile parkinsonism (Kitada et al. 1998) and it has since been identified in a number of other kindreds worldwide. The presence of Lewy body pathology is variable (Ishikawa and Takahashi 1998; Farrer et al. 2001; Gouider-Khouja et al. 2003; Pramstaller et al. 2005) and the parkin protein has been localized to Lewy bodies in sporadic PD (Schlossmacher et al. 2002). *Parkin* encodes a 465-amino acid E3-ubiquitin ligase (Shimura et al. 2000), which can interact with a number of binding partners. Thus, loss-of-function of this ligase activity would be expected to result in disruption of the proteasomal system. Loss-of-function of *parkin* in the mouse has also been shown to induce nigrostriatal dysfunction (Goldberg et al. 2003; Itier et al. 2003; Rodriguez-Navarro et al. 2007; Stichel et al. 2007; Kitada et al. 2009). The parkin ligase has a host of substrates and a recent report examined the role of the loss of parkin function on dopamine neuron survival (Shin et al. 2011), reviewed in (Martin et al. 2011). The authors describe the KRAB and zinc-finger protein, PARIS (ZNF746), as a parkin ligase substrate that modulates the expression of the transcriptional regulator, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). Loss of parkin function leads to the up-regulation of PARIS, which occurs in human PD, repression of PGC-1α and dopamine neuron loss. Further, studies initially carried out in *Drosophila* (Greene et al. 2003; Clark et al. 2006; Yang et al. 2006) and expanded to mammalian systems (*see* Kawajiri et al. 2010; Chan et al. 2011; Kuroda et al. 2012) have provided a link between *parkin*, *PINK1* (see below), mitochondria and autophagy/mitophagy as a potential pathway involved in PD pathogenesis (*see also* Hardy et al. 2009; Martin et al. 2011).

16.2.1.4 Phosphatase and Tensin Homolog (PTEN)-Induced Putative Kinase 1

Mutations in the gene encoding PINK1 (*PARK6*, *PINK1*) were initially identified by Valente and colleagues (Valente et al. 2004) in families with PD that displayed an earlier age of onset, slower progression and more favorable L-DOPA response. A report recently identified Lewy body pathology in one member of a family with *PINK1* mutations (Samaranch et al. 2010). PINK1 is a 581-amino acid mitochondrial kinase with unknown substrates, but this protein is known to be upstream of parkin in the mitophagy pathway. Work by Narendra et al. (2010) suggests that the selective

retention of the PINK1 protein on damaged, depolarized mitochondria leads to recruitment of parkin and ubiquitination of parkin substrates followed by mitophagy. Thus, both parkin and PINK1 are important for normal mitochondria dynamics and loss of function of either can lead to mitochondrial impairment, dopamine neuron loss and parkinsonism.

16.2.1.5 DJ-1

Mutations in the gene encoding the protein DJ-1 (*PARK7*, *DJ-1*) were first identified in two European families (Bonifati et al. 2003), but there have been no reports to date regarding Lewy body pathology in individuals with *DJ-1* mutations. The DJ-1 protein is ubiquitously expressed with strong expression in astrocytes and occasional localization to Lewy bodies in sporadic PD brains (Bandopadhyay et al. 2004; Kumaran et al. 2009). The 189-amino acid protein is multifunctional and has been linked to a number of other diseases in addition to PD, including cancer (reviewed in Wilson 2011). What is clear is that DJ-1 is a redox sensor that can act in multiple roles from a peroxidase (Andres-Mateos et al. 2007) and a chaperone (Shendelman et al. 2004; Zhou et al. 2006) to an RNA-binding protein (van der Brug et al. 2008; Blackinton et al. 2009) and a regulator of mitochondrial integrity (Hao et al. 2010; Larsen et al. 2011; Ren et al. 2011; Thomas et al. 2011). DJ-1 has also been shown to stabilize the antioxidant transcriptional regulator, Nrf2 (Clements et al. 2006). Loss of function in animal models leads to both motoric and dopamine neuron dysfunction (Chen et al. 2005; Goldberg et al. 2005; Lavara-Culebras and Paricio 2007; Pham et al. 2010). While the exact mechanisms of action remain unknown, recent evidence suggests that DJ-1 acts in parallel with the PINK1/parkin pathway in modulating mitophagy (Thomas et al. 2011).

16.2.1.6 Additional Genes Implicated in Parkinsonism

A number of genes have also been identified that are associated with other neurodegenerative diseases that have features of parkinsonism. These include the gene encoding the f-box only protein 7 (*PARK15*, *FBXO7*), which has been linked to an autosomal recessive parkinsonian syndrome with early onset and pyramidal symptoms (pallido-pyramidal or parkinsonian-pyramidal syndrome (Di Fonzo et al. 2009). Fibroblast cell lines in patients from two families with this syndrome appear to have loss of or diminished nuclear Fbxo7 expression (Zhao et al. 2011), although this is only one report. While it is difficult at this point to assign a mechanism or cellular localization of Fbox7 dysfunction, the protein is an SCF E3-ubiquitin ligase (Skp1, Cullins, F-box protein; (Cenciarelli et al. 1999; Hsu et al. 2004; Chang et al. 2006)), putting it in a similar pathway as parkin. Interestingly, Fbox7 regulates a number of substrates, including the human inhibitor of apoptosis protein cIAP1 (Chang et al. 2006) and NF-κB (Kuiken et al. 2012).

Kufor-Rakeb syndrome is an autosomal recessive potential lysosomal storage disease with early onset parkinsonism, pyramidal symptoms and dementia that has been

linked to the gene encoding the lysosomal ATPase, ATPase 13A2 (*PARK9*, *ATP13A2*; Ramirez et al. 2006). ATP13A2 levels are highest in human cortex (pyramidal neurons) and dopamine neurons in the SN, are up-regulated in PD brain and regulate calcium homeostasis and neuron survival (Ramonet et al. 2012). Studies also suggest that ATP13A2 may be important in maintaining mitochondrial dynamics (Gusdon et al. 2011; Ramonet et al. 2012) again providing a link between parkinsonism, mitochondria and parkin, PINK1 and DJ-1. Another autosomal recessive lysosomal storage disease, Gaucher's disease, has also been linked to PD. The disease is caused by loss-of-function of glucocerebrosidase (encoded by *GBA*) with the resultant accumulation of glucocerebrosides within lysosomes. First linked to an increased risk of PD in *GBA* mutation carriers (Goker-Alpan et al. 2004), it has since been demonstrated that *GBA* mutations are associated with both early-onset and idiopathic PD (Clark et al. 2007; Neumann et al. 2009; Sidransky et al. 2009), as well as dementia with Lewy bodies (Clark et al. 2009).

Finally, a number of neurodegenerative diseases are associated with the presence of Lewy bodies, including both the neurodegeneration with brain iron type 1 (Hallervordern-Spatz disease, NBIA1, *PANK2*; Arawaka et al. 1998) and type 2 (*PLA2G6*; Paisan-Ruiz et al. 2012), as well as Niemann-Pick Type C disease (*NPC1*; Saito et al. 2004). Further study may provide additional clues to PD pathogenesis, specifically protein aggregation and Lewy body formation. Hardy and colleagues provide a concise, well-reasoned discussion of these genes and the current state-of-the-art of the genetics of PD (Hardy et al. 2009).

16.2.2 Genetic Risk Factors of Disease

While the past decade and a half of research into the genetics of familial PD has been fruitful, the vast majority of PD cases are sporadic. The technologies that have enabled the post-human genome era have allowed for the comprehensive scanning of SNPs across the genome, allowing for GWA studies for disease risk alleles. Many early GWA studies were underpowered and SNPs associated with disease did not replicate these associations in follow up studies in other case/control populations (*see* Elbaz et al. 2006; Evangelou et al. 2010). Furthermore, differences in allele frequencies in different ethnic populations may also explain the lack of concordance among studies (*see* Satake et al. 2009; Simon-Sanchez et al. 2009). However, many recent large-scale studies with well-controlled discovery and replication phases, coupled with new meta-analyses of these data, have provided interesting insight into genetic risk of PD.

The discovery (Satake et al. 2009; Simon-Sanchez et al. 2009) and subsequent validation (Pankratz et al. 2009; Edwards et al. 2010; Ding et al. 2011; Mata et al. 2011) of *SNCA* as a genetic risk factor for sporadic PD provided additional confirmation, with the *PARK1/4* loci and Lewy body pathology, that this gene/protein is a key contributor to disease. Interestingly, *MAPT*, the gene that encodes the microtubule-associated protein tau (tau) was also identified and validated as a risk allele (Pankratz

et al. 2009; Simon-Sanchez et al. 2009; Edwards et al. 2010; Mata et al. 2011; Rhodes et al. 2011), although there appear to be ethnic differences (Satake et al. 2009). While the tau protein has traditionally be identified with the neurofibrillary tangles observed in AD and other tauopathies, this discovery points to common pathogenic pathways in neurodegenerative diseases. Similar to the *SNCA* locus, *LRRK2* (Satake et al. 2009; Simon-Sanchez et al. 2009; Consortium et al. 2011) has also been identified to contribute to genetic risk of sporadic PD; again, providing additional confirmation that the *PARK8* loci is important in both familial and sporadic disease. Three additional risk alleles have been identified that have been confirmed in other studies, although there may be ethnic differences. The first is *BST1* (Satake et al. 2009; Tan et al. 2010; Consortium et al. 2011; Simon-Sanchez et al. 2011), a gene that encodes ADP-ribosyl cyclase 2 protein (CD157), that had been previously associated with the immune system and signal transduction, including tyrosine phosphorylation and calcium mobilization (Ortolan et al. 2002), which may be important to the neuroinflammation or dopamine neuron sensitivity, respectively. *GAK* (Pankratz et al. 2009; Hamza and Payami 2010; Rhodes et al. 2011; Simon-Sanchez et al. 2011) encodes the protein cyclin G-associated kinase, which is important in clatharin-mediated vesicle dynamics (Ungewickell and Hinrichsen 2007; Lee et al. 2008), is structurally similar and can replace the synaptic protein, auxilin (Yim et al. 2010), and may modulate levels of α-synuclein (Dumitriu et al. 2011). Lastly, variation in the human leukocyte antigen region (*HLA* (Hamza et al. 2010; Consortium et al. 2011; Simon-Sanchez et al. 2011)) provides an additional link between neuroinflammation and PD.

A recent large meta-analysis was conducted on 12,386 PD cases and 21,026 controls from five USA/European GWA studies (Consortium et al. 2011). The first stage of analysis replicated the loci discussed above (*SNCA*, *MAPT*, *LRRK2*, *HLA*, *BST1*, and *GAK*) and identified an additional five loci: *ACMSD*, *CCDC62/HIP1R*, *MCCC1/LAMP3*, *STK39*, and *SYT11* (Consortium et al. 2011). A second stage analysis of the data further revealed five loci: *FGF20/*8p22, *GPNMB*/7p15, *PARK16*/1q32, *STBD1*/4q21, and *STX1B*/16p11. *PARK16* has been previously associated with PD risk (Satake et al. 2009; Simon-Sanchez et al. 2009), although the gene(s) responsible has/have not been identified (Tucci et al. 2010). *FGF20* has also been linked as a risk locus in some populations (van der Walt et al. 2004), but not in others (Clarimon et al. 2005; Wider et al. 2009). However, it is intriguing since this is a central nervous system (CNS) neurotrophic factor. A number of the loci are related specifically to synaptic vesicle dynamics (*HIP1R*, *SYT11*, *STX1B*) or to lysosome/endosome function (*LAMP3*). The remaining loci are related to stress pathways (*STK39*); metabolic pathways (*MCCC1*, *STBD1*), including an enzyme that prevents the conversion of an intermediate to toxic quinolinate in the tryptophan-to-NAD pathway (*ACMSD*); and cancer pathways (*CCDC62*, *GPNMB*). While it is too early to fully appreciate how these genes (or genes that co-segregate with these loci) will fit into even a provisional model of PD pathogenesis, these data do support our current understanding and suggest further research avenues.

The past 15 years have greatly influenced our understanding of genetic contributions to both familial and sporadic PD; however, there are caveats to this progress. First, association in GWA studies does not imply causation; there is always the

impulse to craft an explanation of how a given risk allele can contribute to disease. Until we test specific hypotheses that relate these genes to a biologically relevant pathway, we should not over speculate as to how each gene fits into our understanding of PD. Also, familial cases of disease remain rare and the genetic risk factors identified for sporadic disease provide small to moderate increases in risk. Whether PD will be primarily a disease caused by a small number of common risk genes or a disease of a large number of rare risk genes remains to be known (Scholz et al. 2012). However, genetic profiles will have implications in not only our understanding the biology of disease process, but also in our ability to diagnose, treat and, perhaps, prevent disease. Further, while the traditional linkage analysis studies and the more recent GWA studies are specifically designed as such, they only identify "risk" alleles and do not provide any information regarding the presence of possible "protective" alleles. Understanding why an individual does not develop disease may be as informative as understanding why another individual does develop disease. Furthermore, understanding why one patient progresses rapidly and another seems to have a more benign course will be fundamentally important as well. Finally, as the genomics field evolves, newer technologies and economies-of-scale are bringing into reality the genotyping of individual genomes, which may further revolutionize our understanding of the genetic contributions to PD. However, while our ability to generate large genomic datasets has grown, our ability to store and integrate these data has lagged behind. Future efforts will need to be focused on the development of newer technologies and bioinformatics methodologies if we hope to develop meaningful insight from these data (Scholz et al. 2012).

16.2.3 Environmental Risk Factors of Disease

While genetics may explain upwards of 60 % of disease risk for PD, it has long been known that the majority of cases are sporadic by nature, indicating that there are environmental or lifestyle risks for developing disease. However, only in the last three decades have epidemiological studies sought to systematically determine potential environmental risks for PD. The overall data are complicated by a number of factors, not the least of which is study design. But, the data do provide a compelling argument for the environmental risk of developing disease. Wirdefeldt et al. (2011a) provided an excellent extensive summary and discussion of the epidemiological studies of PD.

The first link of PD to the environment was an early anecdotal report by Davis et al. (Davis et al. 1979) that intravenous (IV) injection of meperidine analogs produced parkinsonism in a 23 year old man. A larger case series of four IV drug users (Langston et al. 1983) and a chemist (Langston and Ballard 1983) identified the compound 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) as a potent dopamine neuron toxicant. MPTP is a blood-brain barrier permeant compound that is converted to the dihydropyridinium ion ($MPDP^+$) by monoamine oxidase B in glia cells (reviewed in (Przedborski et al. 2001b). Auto-oxidation of this compound leads to the

formation of the toxic 1-methyl-4-phenylpyridinium (MPP^+), which is taken up by dopamine neurons via the dopamine transporter, where it presumably acts to inhibit mitochondrial complex I activity, although one study reported that loss of complex I function did not abrogate toxicity in dopamine neurons (Choi et al. 2008). Thus, this provides a link between dopamine neuron sensitivity to mitochondrial disruption, specific genetic defects that cause familial PD (*parkin*, *PINK1*, *DJ-1*) and potential environmental toxicants. Both MPTP environmental exposure and toxicity are rare in humans (Langston et al. 1983; Langston and Ballard 1983; Vingerhoets et al. 1994), but it has become a tool, although recently debated, to model PD in animals. MPTP has been extensively studied *in vitro*, in rodents and in non-human primates and a number of excellent reviews provide discussion to the history and outcomes of these models (Przedborski et al. 2001b; Dauer and Przedborski 2003; Fox and Brotchie 2010). While MPTP models have not recapitulated Lewy body pathology, there appears to be an interaction with α-synuclein. In mice α-synuclein expression is increased following MPTP administration (Vila et al. 2000) and MPTP exposure can lead to oxidative post-translational modifications of this protein (Przedborski et al. 2001a). Increased dopamine neuron loss is observed in transgenic mice that over-express both human wild type and mutated forms of α-synuclein (Richfield et al. 2002; Nieto et al. 2006), although this appears to be complicated by genetic background and experimental design (Dong et al. 2002; Schluter et al. 2003). Knock-out of the α-synuclein gene leads to MPTP-resistance (Dauer et al. 2002). α-Synuclein is also up-regulated, aggregated and oxidatively modified in non-human primate models (Kowall et al. 2000; Purisai et al. 2005; Chen et al. 2008b; McCormack et al. 2008), but there is no development of Lewy body pathology (Halliday et al. 2009).

Following the discovery of MPTP and its toxic effects, a number of epidemiological studies were conducted to identify environmental risk factors of PD. Specifically, the structural similarity between MPTP and paraquat, an herbicide used extensively worldwide, led to a heightened interest in examining pesticide exposure and risk of developing disease. Both general (e.g., rural living, well water use, farming profession, non-specific pesticide exposure, etc.) and exposure to specific pesticides (e.g., specific classes, paraquat, rotenone, etc.) have been associated with PD incidence, although often as many studies refute these associations as support them (*reviewed in* Wirdefeldt et al. 2011a). A number of other environmental factors have also been proposed to increase the risk of PD, including metals, solvents, electromagnetic radiation, head trauma (other than parkinsonism in boxers), viral infections (other than post-encephalitic parkinsonism) and others, but the evidence is tenuous as to whether these factors influences risk of disease.

Two pesticides that have received considerable attention in the study of mechanisms of PD are paraquat, which induces reactive oxygen species (ROS) formation via redox cycling (Bus and Gibson 1984), and rotenone, a mitochondrial complex I inhibitor (Gutman et al. 1970). In better-controlled epidemiological studies both appear to be environmental risk factors for developing PD (Tanner et al. 2011). Paraquat has been extensively studied both *in vitro* (*e.g.* Yang and Tiffany-Castiglioni 2007; Choi et al. 2008; Feng and Maguire-Zeiss 2011) and *in vivo* (*e.g.* Brooks et al. 1999; Manning-Bog et al. 2001, 2002; Norris et al. 2007). While paraquat

exposure has not been shown to foster Lewy body formation, it does accelerate α-synuclein misfolding (Uversky et al. 2001), enhances membrane conductance disruption with dopamine (Feng and Maguire-Zeiss 2011) or proteasome disruption (Yang and Tiffany-Castiglioni 2007) in α-synuclein overexpressing cell lines and accelerates protein aggregation, inclusion formation and neuronal degeneration in transgenic mice that over-express α-synuclein (Manning-Bog et al. 2002; Fernagut et al. 2007; Peng et al. 2010). Rotenone similarly enhances α-synuclein fibril formation in *in vitro* systems, while it increases α-synuclein modification, misfolding and toxicity in cultured cells (Orth et al. 2003; Mirzaei et al. 2006; Borland et al. 2008; Lu et al. 2010; Ma et al. 2011). α-Synuclein aggregation and cell death are also key findings in rodents exposed to rotenone (Betarbet et al. 2006; Feng et al. 2006; Borland et al. 2008). Taken together, epidemiological studies and follow up experimental work suggest that environmental factors that increase oxidative stress or that inhibit mitochondrial function can lead to α-synuclein misfolding and nigrostriatal damage that are reminiscent of PD.

Interestingly, recent studies have identified potential environmental "protective" factors that appear to confer some benefit to decreased incidence of PD, including tobacco use, caffeine use and circulating levels of uric acid (Wirdefeldt et al. 2011a). Both nicotine (Quik 2004) and caffeine (Kalda et al. 2006) have been proposed to be neuroprotective in PD and nicotine itself has been shown to inhibit α-synuclein fibrillization (Ono et al. 2007). Higher plasma urate levels have been associated with decreased incidence of PD (Weisskopf et al. 2007; Winquist et al. 2010) and with a decreased rate of decline in PD patients (Schwarzschild et al. 2008; Ascherio et al. 2009), perhaps providing an additional link to the protective effects of caffeine and the purinergic system (Morelli et al. 2010). Although it is easy to over-emphasize the importance of potential environmental "protective" factors or the discovery of genetic "protective" factors, these studies and future work should provide insight into potential strategies that can slow, halt or even prevent PD.

The epidemiology of environmental risk factors for PD also suffers from the same caveats discussed above for the genetic risks. Namely, association does not imply causation; it is difficult to ascertain exposure history, especially in retrospective studies; these factors impose small to moderate risks; and the etiology of the disease itself suggests that there are probably multiple genetic, environmental and perhaps stochastic factors that will interact in complex ways to initiate and propagate disease. However, while no definitive environmental risk factor has been identified, the compounds discussed above have proven to be important research tools in probing the mechanisms of disease, especially in terms of protein misfolding, mitochondrial toxicity, oxidative stress and inflammation.

16.3 Pathological Features of PD

The hallmark pathological features of pure PD are the invariant progressive loss of SNpc dopamine neurons and the presence of intracytoplasmic eosinophilic inclusion bodies (Lewy bodies) in the remaining neurons in this region. Approximately

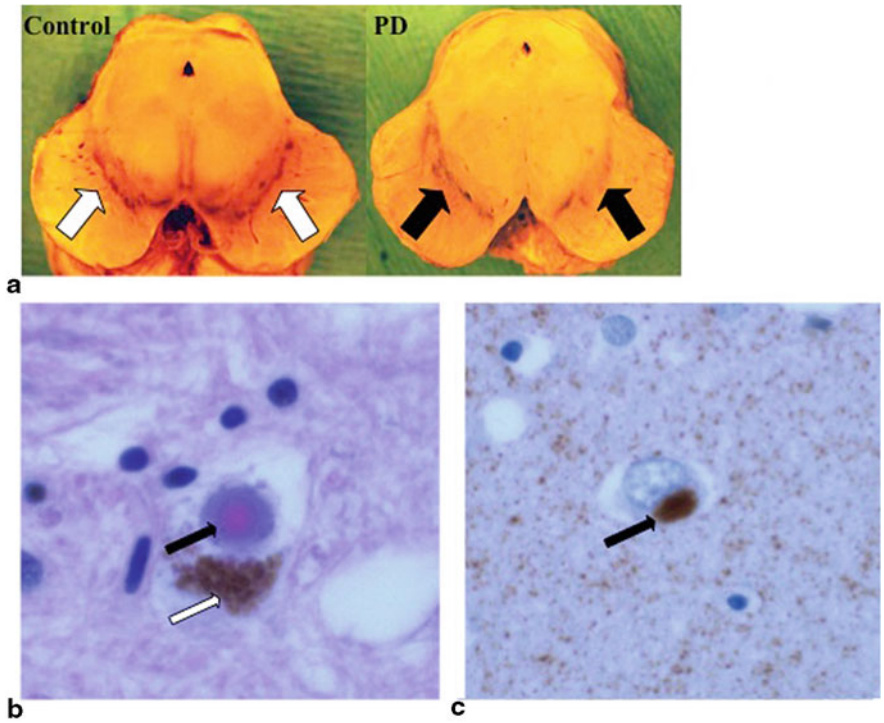

Fig. 16.1 Typical Parkinsonism and Lewy Pathology. **a** Human midbrain image demonstrating loss of SNpc dopamine neurons in a PD subject. The midbrain was grossly dissected away from control (*left*; non-PD) and PD (*right*) brains. The white arrows indicate the right and left SNpc in a non-PD subject. Note the loss of pigmentation in the PD subject (*black arrows*) indicating a decreased number of melanin containing dopamine neurons. The image in Panel A was kindly contributed by Drs. Nabil Azzam and Rebekah Feng, Department of Neuroscience, Georgetown University College of Medicine. **b** H&E staining of a prototypical Lewy body in a SNpc dopamine neuron. Note the pink proteinaceous intracytoplasmic inclusion body (*black arrow*) within a SNpc dopamine neuron resulting in displacement of the normal brown pigmented melanin (*white arrow*). **c** Immunohistochemical staining for α-synuclein-positive Lewy bodies: seven micron thick, paraffin-embedded sections of cortex were labeled with an antibody directed against human α-synuclein. Note the intense brown labeling of the intracytoplasmic inclusion (*black arrow*). Images in Panels B & C are from a DLBD patient and were kindly contributed by Dr. William W. Pendlebury, University of Vermont College of Medicine. Brain tissue was kindly provided by the Georgetown University Medical Center and the University of Vermont College of Medicine Anatomical Gift Programs

60–70 % of SN dopamine neurons are lost in PD patients at the presentation of motoric symptoms; therefore, at the end-stage of disease one can appreciate the profound loss of these pigmented neurons (Fig. 16.1; Panel A). Lewy first described intraneuronal proteinaceous inclusions in 1912 where he identified them in brain sections from patients with idiopathic paralysis agitans (the history of the Lewy body is reviewed in (Holdorff 2006; Rodrigues e Silva et al. 2010)). The Russian neuropathologist

Konstantin Tretiakoff coined the term "corps de Lewy" to describe these inclusions in his thesis on the SN as a tribute to Lewy's first observation (Rodrigues e Silva et al. 2010). However, according to Rodrigues e Silva, Lewy and Tretiakoff disagreed on the primary locus of PD with Lewy suspecting that the pallidum, not the SNpc, as the primary site of degeneration. Another description confirming the SN as a primary site of neuronal loss in PD was reported by Rolf Hassler in 1938. However, the presence of Lewy bodies did not become the standard for post-mortem diagnosis of PD until after Lewy's death. Currently, the presence, number and specific anatomical localization of Lewy bodies as well as Lewy neurites, proteinaceous inclusions within neuronal projections, are used for the post-mortem diagnosis of PD (den and Bethlem 1960; Braak and Braak 2000; Braak et al. 2002, 2003, 2004, 2006).

The observation of intracytoplasmic eosinophilic inclusions within the brain of PD patients was initially made following post-mortem histological staining. In Fig. 16.1, we show a typical Lewy body inclusion in the SNpc following staining of brain sections with hematoxylin and eosin (H&E stain; Panel B, black arrow). However, the biological composition of Lewy bodies remained a mystery until 1998 when Spillantini et al. (1997) determined that a major component of this complex in addition to ubiquitin was α-synuclein (Fig. 16.1; Panel C, black arrow). As mentioned above, mutations and multiplications of the gene encoding α-synuclein cause familial PD and importantly GWA studies link this protein to sporadic/idiopathic forms of this disease. However, there are subgroups of PD patients that do not exhibit any α-synuclein pathology. Furthermore, α-synuclein-positive Lewy bodies are found in other disorders, known as synucleinopathies, which in addition to PD include diffuse Lewy body disease (DLBD), Lewy body dementia (LBD) and multiple system atrophy (MSA) (Spillantini and Goedert 2000; Schulz-Schaeffer 2010). These observations suggest that Lewy pathology (and in particular misfolded α-synuclein), while affecting different subtypes of neurons as well as glia, may represent a common thread between these neurodegenerative disorders (Fig. 16.1; Panel C). In any case α-synuclein immunohistochemistry is the most common histological stain used for the identification of Lewy bodies and Lewy neurites in PD and other synucleinopathies. Further analysis of Lewy bodies determined that a portion of the α-synuclein found in Lewy bodies is phosphorylated on serine 129 and ongoing research is aimed at determining the role of this phosphorylation in α-synuclein-induced pathology (Fujiwara et al. 2002).

Heiko Braak's group has extensively studied Lewy pathology in different clinical stages of typical idiopathic PD using α-synuclein immunohistochemistry (Braak and Braak 2000; Braak et al. 2002, 2003, 2004, 2006; Braak and Del Tredici 2008). Their observations reported in 2003 suggest that α-synuclein pathology follows a caudo-rostral progression with areas such as the olfactory bulb, enteric nervous system and brain stem affected early in the pre-motor stage of disease followed by the pigmented locus coeruleus (Braak et al. 2003). The SNpc, most often associated with the motoric symptoms of PD, becomes involved later at approximately stage 3 of 'Braak and Braak'. Finally, cortical pathology is most intense at the end stage of disease, displaying intracytoplasmic α-synuclein-positive neuronal inclusions, dystrophic α-synuclein-positive Lewy neurites as well as some astrocytic inclusions. Braak went on to propose that PD might progress as a type of "prion-disease" with an

environmental/pathogenic factor initiating disease (*e.g.*, α-synuclein misfolding) at the level of the olfactory bulb and/or gut and slowly progressing to the CNS. However, as not all post-mortem cases follow this progression, some affected brain regions do not strictly follow the proposed caudo-rostral progression, and there are reports of the presence of α-synuclein pathology in patients that do not suffer from PD, this theory remains under investigation (Burke et al. 2008; Kalaitzakis et al. 2008; Dickson et al. 2010; Goedert et al. 2010; Jellinger 2010). In fact at the 2012 XIX World Congress on Parkinson's disease and Related Disorders in Shanghai, China, an entire forum entitled "What about Braak?" was offered on this topic. The reader is referred to several papers that discuss the aptly named "Braak Staging" of PD (Braak et al. 2003; Hawkes et al. 2010; Halliday et al. 2011; Puschmann et al. 2012).

Despite the ongoing debate as to whether α-synulcein Lewy pathology portends PD progression, the work of Del Tredici and Braak has been the driving force behind a number of studies aimed at identifying peripheral tissues that are both facile to biopsy and predictive of PD (Jain 2011). For example, several groups have shown the presence of α-synuclein Lewy pathology in colonic mucosa and in some cases this precedes the later diagnosis of PD, suggesting that colonic biopsies might provide an accessible biomarker tissue source (Lebouvier et al. 2008, 2010a, b; Wakabayashi et al. 2010; Shannon et al. 2012). Other groups, including an author in this book, Omar El-Agnaf, are using ELISAs to quantify α-synuclein oligomers in CSF and blood as a potential biomarker for PD. In addition, the identification of misfolded α-synuclein in living patients is an ongoing goal in the field of neuroimaging. For example Itoyama's group was able to visualize α-synuclein deposits in the brain of MSA patients using a ^{11}C-labeled positron emission tomography (PET) probe previously shown to bind β-amyloid deposits (2-[2-(2-dimethylaminothiazol-5-yl)ethenyl]-6-[2-(fluoro)ethoxy]benzoxazole [BF-227] (Kikuchi et al. 2010). Imaging studies with large cohorts of PD patients at different H&Y stages (*vide infra*, (Hoehn and Yahr 1967)) are obviously needed to push this technology forward. Additionally, a comparison of PD patients with other neurodegenerative disorder patients will be required to determine the value of this imaging technique for diagnosis, monitoring disease progression and monitoring therapeutic efficacy of treatments.

Although the major focus of PD pathology has been on the loss of SNpc dopamine neurons, other monoaminergic neurotransmitter systems (norepinephrine, acetylcholine, serotonin) are also profoundly affected in PD. Once again the elegant studies from Braak's group illuminate the widespread nervous system devastation of this disease as they describe Lewy body/neurite lesions in neurons outside of the dopaminergic nigrostriatal system, including but not limited to neurons in the dorsal motor nucleus of the vagus, vasoactive intestinal peptide-containing motoneurons, layer I of the spinal cord, the locus ceruleus, the basal forebrain, the central subnucleus of the amygdala and the cerebral cortex (Braak and Del Tredici 2008). These neurotransmitter systems in both the CNS and peripheral nervous system, along with the clinical relevance of the pathological findings, are discussed in more detail in the clinical section of this chapter.

In addition to the profound loss of SNpc dopamine neurons and the presence of Lewy pathology PD post-mortem brains also display increased gliosis (McGeer

et al. 1988; McGeer and McGeer 2008). Gliosis refers to an increase in the number as well as the activation state of astrocytes and microglia. Both of these glial cell types can respond to injury or damage with changes in their morphology and production/secretion of inflammatory molecules (Colton 2009; Colton and Wilcock 2010). The different activation states of glia and their effect on the local microenvironment are active areas of neurodegeneration research, which is outside the scope of this chapter and the reader is referred to the following papers (Colton and Gilbert 1993; Colton et al. 2000; Benveniste et al. 2001; Orr et al. 2002; Liu and Hong 2003; Teismann et al. 2003; Campbell 2004; Carson et al. 2004; McGeer and McGeer 2004; Croisier et al. 2005; Cagnin et al. 2006; Griffin 2006; Kim and Joh 2006; Bartels and Leenders 2007; Block et al. 2007; Dheen et al. 2007; Klegeris et al. 2007; Whitton 2007; Lee et al. 2009; Beck et al. 2010; Graeber and Streit 2010; Olson 2010). McGeer et al. (1988) have reported an increase in the human class II major histocompatibility complex antigen, HLA-DR, positive microglia within the SN of post-mortem PD brains. This observation of increased numbers of activated microglia in regions of degeneration is not unique to PD, as it also occurs in other disorders such as AD, other synucleinopathies and following trauma (McGeer and McGeer 2004; McGeer et al. 2005; Croisier and Graeber 2006; McGeer and McGeer 2008). Furthermore, the number and location of activated microglia in PD and PD-related disorders does not always correlate with the presence of Lewy bodies, nor is glial activation restricted to the nigrostriatal pathway (Rozemuller et al. 2000; Imamura et al. 2003; Croisier et al. 2005). It is interesting, however, that live imaging data from PD patients, using a PET ligand that binds to the peripheral type benzodiazepine receptor, which is up-regulated on activated microglia, positively correlated with disease progression (Ouchi et al. 2005, 2009). In the Ouchi study these authors also demonstrated a negative correlation with a dopamine transporter marker and disease progression (Ouchi et al. 2005, 2009). Furthermore, the microglial activation was not restricted to the nigrostriatal pathway but was evident throughout the brain, suggesting a generalized increase in neuroinflammation in PD. As mentioned previously, one GWA study identified an HLA locus as a risk factor for sporadic PD, further supporting a role of the innate immune system in this neurodegenerative disorder (Hamza et al. 2010). Finally, several studies using cell culture and animal models of α-synuclein overexpression demonstrate that misfolded forms of this protein can directly activate microglia further linking α-synuclein and neuroinflammation to PD (Zhang et al. 2005; Klegeris et al. 2008; Maguire-Zeiss et al. 2008; Reynolds et al. 2008; Su et al. 2008; Theodore et al. 2008; Su et al. 2009; Lee et al. 2010; Beraud et al. 2011).

In conclusion the major neuropathological features of PD are the loss of SN dopamine neurons, the presence of α-synuclein containing Lewy bodies and neurites in the SNpc and an increase in activated microglia. Although we have emphasized the features of pure PD the fact remains that PD patients are not all the same and this disease represents a multifaceted syndrome, which muddies the waters both in terms of clinical and pathological evaluations. For example there are examples of parkinsonian patients that do not have any Lewy pathology or that have profound tau-positive tangle pathology, while pure PD is not associated with tau pathology

(*reviewed in* Wray and Lewis 2010). Therefore, it is essential that the pathological analysis of both the peripheral and central nervous system of parkinsonian subjects be correlated with imaging and clinical data to establish a more complete picture of these complex diseases.

16.4 Parkinson Disease: An Evolving Clinical Phenotype

As discussed above, burgeoning knowledge continues to expand the pathology, pathophysiology, pathobiology and genetics of PD and the clinical phenotype has expanded in parallel from the initial concept of PD as the paradigmatic motor system disorder, secondary to loss of SN neurons and an attendant depletion of the neurotransmitter dopamine in the striatum, to a clinical picture that includes a wide range of autonomic, behavioral, cognitive, olfactory, sensory, sleep and visually related dysfunctions, now encapsulated in the moniker, "Non-Motor Manifestations of Parkinson disease." In James Parkinson's classic monograph entitled "An Essay on the Shaking Palsy" (Parkinson 1817), he noted the gradual onset of the disease, ". . . almost imperceptible are the inroads of this illness. . . " and although his descriptions of the unilateral onset, tremor, rigidity, postural and gait difficulties and disease progression have been amplified, he fully recognized and described very well the core motor features almost two centuries ago (Parkinson 2002; Kempster et al. 2007). Missing from Parkinson's wonderfully written essay are the "Non-Motor Manifestations"; likely because the motor symptoms were so dominant, treatments were non-existent and life expectancy was severely limited. His statement, ". . . the sense and intellect are uninjured. . . ", implies that sensory systems are spared and cognition remained sentient—the mind clear as the body became increasingly immobile with inanition, a more than frightening experience to even consider. Fortunately, with the advent of a wide range of therapies life expectancy with PD approaches that of age-matched controls, although functional capabilities decline and substantial morbidity may ensue.

As previously described, approximately 90 % of PD is sporadic, but the discovery that specific genes (both causative and risk associated) underlie the development of PD has kindled new approaches to understanding both the clinical and neuropathological characteristics of the disorder, as well as approaches to understanding pathogenesis and treatment. For instance the discovery that familial PD is linked to missense mutations (A53T, A30P, E46K) in the synuclein gene (Polymeropoulos et al. 1997; Kruger et al. 1998; Zarranz et al. 2004) led to the development of immunocytochemical methods that revealed α-synuclein to be the major constituent of the 'Lewy body ' in both sporadic and genetic variants of PD. α-Synuclein contributes to the cytoplasmic and nuclear accumulations in neurons and glia in a range of disorders: MSA, DLBD, LBD, NBIA1 and amyotrophic lateral sclerosis (Kruger et al. 2000). It is apparent that synuclein pathology underlies a range of neurodegenerative disorders and the term 'synucleinopathies' was coined (Spillantini and Goedert 2000;

Galvin et al. 2001). Thus, PD is no longer a single nosological entity and along with the aforementioned diseases, is now considered a multisystem α-synucleinopathy.

As already noted, mutations in α-synuclein were the first causative genes linked to PD and subsequent studies of familial PD expanded the number of loci involved into the 'double digits'. Importantly these studies confirmed the clinical heterogeneity of the disorder (Hardy 2010; Devine et al. 2011). The clinical picture ranges from 'fairly classic pictures' in patients with LRRK2 mutations, which may underlie 2 % of adult onset PD, to patients with recessive forms of PD demonstrating onset at a younger age, unusual patterns of tremor upon presentation and relatively slow progression, to varying clinical pictures in families with mutations in the α-synuclein gene. Heterogeneity was apparent in the families described originally by Polymeropoulos (Polymeropoulos et al. 1997) and is amplified by reports of families with triplication and duplication of the synuclein gene (Singleton et al. 2003; Singleton et al. 2004). The association of dementia with fluctuating cognitive impairment, delusions and hallucinations (primarily visual) along with 'basal ganglia features' defines the clinical disorder DLBD. This DLBD picture occurs in some family members within these kindreds, whereas others manifest a more typical PD picture and yet others experienced dysautonomia and a MSA picture evolved. As expected, patients with triplication of the gene experienced a more severe and rapidly progressing illness with life expectancy of approximately eight years (Waters and Miller 1994; Muenter et al. 1998). Essentially a gradient of disease heterogeneity, severity and progression tends to follow gene dosage, although 'typical PD' occurred. Since penetrance in the families with duplication of the synuclein gene is estimated to be 40–45 %, asymptomatic carriers existed within these families as well. Similarly, individuals with the LRRK2 gene may not develop the PD clinical phenotype. Apparently, intrinsic vs. extrinsic factors (genetic vs. epigenetic vs. both) modify the pathobiology and phenotype of the 'Parkinsonian Syndrome' that emerges or fails to do so.

Over the last decade emerging clinical and neuropathological data in humans with PD have resulted in new concepts regarding disease onset and evolution and the once primacy of striatal motor dysfunction as the presenting clinical manifestation is now viewed as part of a continuum of clinical dysfunction. That is, neuropathological changes within the SN may appear as Stage 3 in an evolving caudal to rostral pattern and there is substantial likelihood that PD's initial onset may occur within the hindbrain and/or peripheral autonomic nervous system (ANS) (Braak and Braak 2000; Braak et al. 2003, 2004; Braak and Del Tredici 2008; Dickson et al. 2009). Furthermore, clinical disorders of sleep—Rapid Eye Movement Behavioral Disorder (RBD) [presumably secondary to diseased sleep system neurons in the hindbrain—lateral dorsal tegmental and subceruleus nuclei—Stage 2 of Braak & Braak] and gastrointestinal (GI) and genitourinary (GU) dysfunctions [presumably related to diseased peripheral ANS neurons in enteric and major pelvic ganglion and dorsal motor nucleus of the vagus (Stage 1)] and changes in olfaction (Stage 1) are observed before the classic motor phenotype of tremor and rigidity emerge. In addition as the pathological processes move more rostrally and supratentorially (Stages 4, 5, 6) within the CNS the clinical picture expands to the more vexing aspects of behavioral and cognitive disorders that alter higher integrative functions and create

Table 16.1 Summary of the NMS and Braak stages of pathology

Nonmotor Category	Braak Stage Neuropathology	Neuronal Substrate	Symptoms/Signs
Sensory			
Olfaction	1	Olfactory bulb Anterior olfactory nucleus	Hyposmia Decreased odor detection Decreased identification and discrimination
Pain	2,3	Serotonergic pathways Dopaminergic pathways	Vague discomfort Burning pain Paresthesias
Autonomic			
Gastrointestinal	1,*	DMV *Enteric ganglia	Nausea, constipation Decreased gastric emptying Colonic dysmotility Esophageal dysmotility
Genitourinary	2,**	"Gain setting neurons" **Pelvic autonomic ganglia	Urinary frequency, urgency Incontinence Erectile dysfunction
Cardiovascular	1,***	DMV ***Sympathetic ganglia	Orthostatic hypotension
Thermoregulatory	3,4	Sympathetic ganglia (sudomotor) Hypothalamus	Hyperhydrosis Hypohydrosis/Anhydrosis
Sleep Disorders	2,3	Locus ceruleus subceruleus Raphe nuclei PPN Suprachiasmatic nucleus	Sleep cycle disruption Excessive daytime sleeping RBD
Behavioral Disorders	2,3	Locus ceruleus Raphe nuclei Ventral tegmental area (VTA)	Apathy Depression Anxiety
Dementia	4,5,6	Dopaminergic (SN, VTA) Cholinergic (Nucleus basalis of Meynert) Cortical/LB Pathology subcortical	"Bradyphrenia" Dysexecutive syndrome Memory decline Visuospatial impairment

extremely challenging management issues (Table 16.1). Collectively, clinical and neuropathological data suggest the possibility that clinical symptoms and disease pathology may present and progress in a somewhat parallel fashion from structures that are involved quite early and contribute to the premotor phenomena (peripheral autonomic structures; olfactory bulb and dorsal motor nucleus of the vagus—Stage 1;

brainstem gain setting systems—Stage 2) to areas that are associated with the onset of the classic motor presentation (midbrain and diencephalic structures—Stage 3) to involvement of higher subcortical and cortical structures (Stages 4, 5, 6). Thus, the clinical phenotype of PD may evolve in somewhat of an inverse hierarchical fashion: peripheral to rhombencephalon to mesencephalon to diencephalon to limbic and telencephalic neocortical structures. However, it is important to recognize that the disease remains heterogeneous; not all patients exhibit the full-blown motor and non-motor disorder with a portion of patients exhibiting motor components that remain somewhat restricted for many years and cognitive and behavioral functions that appear normal or are only minimally affected. Clinical features are still most easily viewed as motor and non-motor components of the PD phenotype discussed below.

16.4.1 Clinical Features

16.4.1.1 Motor Symptoms

The classic unilateral features of PD emerge when dopamine depletion in the contralateral striatum reaches 30–40 % of normal. A straightforward acronym—TRAP—serves to delineate the tremor, rigidity, akinesia and postural changes that comprise the initial motor symptoms. Tremor, typically in the 3–5/4–6 HZ range, occurs unilaterally and at rest and is generally distal in character; forearm, hand, fingers or foot. The tremor abates with activation of the involved limb and may be accentuated with activation of other body parts, with walking or with stressful situations (mental status testing, for instance). In about 60–70 % of patients tremor is the first symptom that appears and over time extends to the ipsilateral lower limb or to the contralateral upper limb. Tremor may involve the jaw, tongue, head or trunk and at times may be felt within the abdomen without any external evidence of axial tremor. Tremor limited to the head is unlikely to be PD. Rigidity, increased muscular tone at rest as well as with resistance to passive stretch, is present in both flexor and extensor muscles and is usually present unilaterally at the onset of the illness. Flexor tone generally exceeds extensor tone so that the involved limb may be positioned differently (*vide infra*). Passive movement of a contralateral limb (Froment's Maneuver) may be necessary to reveal the increased tone (rigidity). Occasionally, passive movement is interrupted in a 'cog-wheel' fashion, reflecting the underlying oscillation of a 3–5 HZ tremor. Of note, occasionally the frequency of cog-wheeling appears at 8–10 HZ in the range of physiological tremor as may be seen in advanced essential tremor (ET), providing a challenge in separating ET and PD in elderly patients. Akinesia (permits TRAP to be spelled) includes *both* hypokinesia and bradykinesia. Hypokinesia implies reduced amplitude and frequency of movements, whereas bradykinesia reflects slowness of movements. Both underlie the poverty of normal resting and associated movements. Common hypokinetic observations include reduced blinking rate and facial expression (reptilian stare and hypomimia), reduced arm swing on walking

and absence of associated movements when arising from a chair or bed. Bradykinesia results in reduced speed of movements (both initiation and execution), slowness in rapid alternating movements such as finger tapping and open and closing a hand (fist) or toe tapping and altered fine motor control and dexterity with impaired writing, buttoning, tying shoes, etc. Many patients report weakness in the limb that is involved, but strength testing is usually normal and the perception of weakness is secondary to the bradykinesia that impairs activation of muscle groups and reduces the force of contraction. Postural changes involve body positions and gait; postural instability is *not* a feature of early PD. Postural changes may be subtle at onset and include a flexed posture of the head and shoulders. The involved limb is slightly flexed at the elbow, wrist and fingers, suggesting an upper motor neuron lesion such as a stroke (flexor tone predominates). Over time both upper extremities develop a flexed posture. Upon standing the base is somewhat narrow but balance is maintained with a negative Romberg test. Upon walking arm swing is reduced and the person may turn 'en bloc.' The involved limb will swing less and there is a reduced range of motion at the shoulder that may lead to glenohumoral capsulitis (a.k.a. frozen shoulder syndrome) and other joint pathology if not recognized and intervention planned. The gait is short stepped (reduced stride length) and upon turning there is gait decompensation with a number of short steps inserted to complete the turn. Walking down a slope may result in difficulty controlling forward speed and patients experience more rapid forward steps (festination) and may actually have difficulty stopping (propulsion); they seem unable to take a long step to stop forward motion. Similarly, walking an upgrade may generate the sense that one might start going backward (retropulsion). While standing, patients may experience a sense of being pulled forward or back and move forward or back with short steps to steady themselves. Importantly, early in the course postural reflexes are relatively preserved and spontaneous falls do not generally occur, but rather are precipitated by tripping or other events. Falling as a prominent early feature suggests a Parkinson-like disorder, such as progressive supranuclear palsy, and is a 'red flag' indicating a search for another neurological disease is in order. Fortunately, the classic motor difficulties generally respond quite well to treatment early on: patients may become functionally asymptomatic. Unfortunately, as the disease progresses over time, medications are less effective as neuronal loss and multisystem neurodegeneration proceeds. Failure to initially respond to dopaminergic therapies is another 'red flag' and makes the clinician rethink the diagnosis of PD.

The underlying pathophysiology of motoric features in PD has been extensively studied. A number of publications provide detailed reviews of potential mechanisms underlying the clinical manifestations (Bergman and Deuschl 2002; Nambu 2008; Rodriguez-Oroz et al. 2009; Wichmann and Dostrovsky 2011). Discussion of the key aspects of the functional neuroanatomy and neurophysiology begins in the mesencephalon. Regardless of the applied model of basal ganglia function, neuronal degeneration in the SNpc and loss of dopaminergic regulation of the striatum is the nidus for a complex derangement of motor regulation resulting in clinical parkinsonism. The classical Albin-DeLong 'rate model' of the direct and indirect pathways of cortical-basal ganglia-thalamo-cortical closed-loops provided the basis for dramatic

expansion in understanding basal ganglia physiology. In this basic model the striatum serves as an entry point for cortical projections into the basal ganglia (Alexander et al. 1986; Albin et al. 1989; Alexander et al. 1990; DeLong 1990). In PD striatal dopamine depletion causes deactivation of the excitatory D1 direct pathway and hyperactivation of the inhibitory D2 indirect pathway. PD-related pathological changes in this model are supported by electrophysiological evidence of increased firing rates in the globus pallidus internal (GPi), SN reticulata (SNr) and subthalamic nucleus (STN) and reduced firing rates in globus pallidus external (GPe) seen in human and MPTP-treated monkeys and by the relative normalization of these changes with dopamine replacement therapies (Bergman and Deuschl 2002). The end resultant change in these two pathways is internal pallidal inhibition of thalamocortically generated voluntary movement. More recently, expanded electrophysiological and metabolic data have revealed the limitations of the 'rate model'. There has been a shift in theory to far more complex interactions and alterations in neuronal activity, including firing rates and patterns, oscillatory synchrony and synaptic plasticity (Nambu 2008; Wichmann and Dostrovsky 2011). Additionally, the classic 'rest tremor' of PD remains insufficiently explained by the aforementioned basal ganglia model alone. PD tremor severity correlates poorly with the other cardinal symptoms and degree of dopamine deficiency. As a result, 'rest tremor' inconsistently responds to dopamineric therapy in a dose-dependent fashion. This classical feature of PD is suspected to originate from a trigger in the basal ganglia with contributions from cerebellothalamic pathways (Hallett 2012). Such a hypothesis is supported clinically by the successful amelioration of tremor with high frequency stimulation of the ventral intermediate nucleus of the thalamus (ViM).

The pathophysiology of the other major motoric phenomena of PD (rigidity, akinesia [hypokinesia/bradykinesia], postural instability) are similarly complex. Since studies in laboratory animals, whether primate or rodent, vary depending on the model being explored, and studies in humans generally have been at late stages of the disease, it is not surprising that data vary and interpretations of cause and effect are challenging. Akinesia likely reflects the altered firing pattern within the indirect and direct pathways and the resulting increased activity in GPi/SNr that inhibits thalamocortical projections and secondarily reduces activity in the motor system neurons in the cortex. The slowed motor phenomena of PD are the symptoms complex that responds best to dopamine replacement or agonist therapy. Rigidity also may be explained by the overall hypothesis that altered firing rates within the basal ganglia are fundamental to disease manifestations. Apparently, since the basal ganglia function to direct and coordinate movements by initiation and termination of specific motor programs, and since the synchrony of the movements require precise integration of signals so that interfering motor programs are suppressed, the altered tone (hypertonicity) may manifest competing agendas of movement. That is, the eventual output of the cortical and subcortical motor system in PD alters supraspinal input to spinal motor neurons and results in inappropriate activation of agonist and antagonist muscles with resultant bradykinesia and 'Lead pipe' rigidity.

Needless to say, these clinical interpretations of motor phenomena are overly simplistic in light of the reciprocal cortical loops referenced above (loops that include

motor, associative and limbic circuits that are involved in planning and execution of motor movements, learning and working memory, and emotions), and the integration of cerebellar pathways both within the thalamus and cortex that in turn influence cortical projection back to the striatum and the supraspinal effector system. More recently, brainstem pathology in patients with PD has been recognized as a major contributor to the clinical phenomena of PD. The altered postural control difficulties with imbalance, falls and freezing of gait that tend to occur late in PD appear to reflect neuronal degeneration and dysfunction within cholinergic systems outside of the basal ganglia. The pedunculopontine nucleus (PPN), a nucleus in the rostral pontine mesencephalic junction, is largely cholinergic and projects to the basal ganglia and other rostral motor control systems (Jenkinson et al. 2009; Karachi et al. 2010). These neurons degenerate and die in PD and the extent of this pathology appears to relate to the akinetic as well as the postural difficulties in PD (Hirsch et al. 1987; Zweig et al. 1989). Imbalance with frequent falls and freezing of gait are not very responsive to dopaminergic agents. Recently, studies in selected PD patients demonstrate that stimulation of the PPN improves locomotion with reduced falls and gait freezing (Thevathasan et al. 2011).

16.4.1.2 Non-Motor Symptoms (NMS)

The frequency of symptoms outside the motor phenomena of PD is substantial; collectively a range of symptoms including autonomic, behavioral (Neuropsychiatric-depression, psychosis), cognitive, olfactory, sensory and sleep disorders occur in 80–90 % of patients with PD (Shulman et al. 2001, 2002). These disorders have been reviewed extensively (Chaudhuri et al. 2006; Pfeiffer 2007; Simuni and Sethi 2008; Tolosa and Poewe 2009; Gallagher et al. 2010; Lim and Lang 2010). The non-motor symptoms may manifest before, coincident with or after the classic motor symptoms of the disease emerge. These non-motor symptoms and dysfunctions are important to recognize as possibly heralding PD since they may identify patients early, especially if disease-modifying therapies are developed. Furthermore, of major practical significance is the fact that many times these symptoms are associated with more impairment in daily life (quality of life, QOL) than motor dysfunction (Gallagher et al. 2010). This study provides a very comprehensive assessment of the range of NMS and their relationship to QOL outcomes. Importantly, the prevalence of cognitive, autonomic and mood disorders was high and impacted QOL more than motor dysfunction. In general progression of these clinical problems may result in patients requiring care in a supervised environment. The following discussion will highlight selected components of the disorders that reflect involvement of 'Non-motor' neuronal systems.

Behavioral/Neuropsychiatric Disorders

Cognitive decline (dementia) and altered mood (depression) are two of the most common disorders of higher cortical function affecting patients with PD; both

disorders may manifest in approximately 30–40 % of patients. Prevalence data for these entities report wide variations, which likely reflect methodological differences. For instance demographic data for dementia is influenced by such factors as: definitions and inclusion criteria, treated vs. untreated patients, stage of the disease, varying age groups and confounds of coincident AD and DLBD vs. PD dementia (PD-D). Similarly, for depression or behavioral change the following clinical features will influence the composition of the epidemiological data sets: premorbid 'Parkinson Personality,' anxiety and apathy, fatigue, amotivational syndromes and severe vs. mild depression vs. adjustment reactions. A number of excellent studies over the last 25 years have described the epidemiological and phenomenological characteristics and longitudinal course, diagnosis and management of these vexing disorders (Mayeux et al. 1981; Brown and Marsden 1984; Raskin et al. 1990; Cummings 1992; Shulman et al. 2001; McDonald et al. 2003; Aarsland et al. 2005; McKeith et al. 2005; Stout and Johnson 2005; Emre et al. 2007; Weintraub and Burn 2011; Aarsland et al. 2012).

Cognition/Dementia

Screening tests for cognitive impairment in early PD are generally unrevealing, although there are reports of mild cognitive changes in approximately 25 % of non-demented PD subjects (Aarsland et al. 2010). In addition more detailed neuropsychological examination early in the course of the disease will likely reveal subtle changes in cognitive function. Classic teaching notes that subjects with PD-D exhibit impairments in the following cognitive domains: attention, executive functions, memory, visuo-spatial perception and construction. Not unexpectedly, patients with PD, DLBD and AD will exhibit similar and overlapping deficits on neuropsychological testing. There is general agreement that as these diseases progress, patients will demonstrate deficits that are more similar and overlapping than different and distinguishing. Nevertheless, cognitive data in the initial stages of disease suggest that subjects with PD-D will predominantly exhibit deficits in executive function and visuo-spatial perception and construction, whereas subjects with AD will demonstrate early deficits in memory and language. Thus, a 'subcortical' (dys-executive) vs. a 'cortical' phenotype is somewhat ingrained as a hallmark of separating PD-D vs. AD. Differentiating PD-D from AD and from DLBD is not consistently and reliably achieved by neuropsychological testing alone with the overlap greatest between PD-D and DLBD.

As cognitive changes, however subtle, may be present early in the course of the disease, and since a substantial percentage of PD patients will progress to PD-D (up to 80 % as patients live longer with the disease; Aarsland et al. 2003) investigators have examined whether specific aspects of cognitive dysfunctions which might predict whether dementia will ensue or might herald the shift from mild cognitive changes to dementia. Stern and colleagues identified that memory dysfunction, including delayed-recall memory and decline on confrontational naming, changed substantially as the clinical deficits expanded to dementia (Stern et al. 1993, 1998). Williams-Gray and colleagues suggested that three baseline measures (age >72, impaired semantic

fluency and visual construction) are predictors of dementia risk with an odds ratio of 88 within the first five years of diagnosis (Williams-Gray et al. 2009). These authors present an interesting hypothesis that frontal executive impairments, clearly evident in early PD, may more clearly relate to altered prefrontal dopaminergic activity and COMT (Catechol-O-MethylTransferase) phenotype and not necessarily presage dementia. Posterior cortical impairments (visual percepts and constructs) may more clearly relate to *MAPT* genotype and Lewy body pathology that more likely herald PD-D.

Non-cognitive domains of neurological dysfunction also are associated with an increased risk for dementia. Increased age and a motor phenotype of increased rigidity and impaired gait and balance are associated with a higher risk of dementia (up to tenfold). Patients with predominant tremor, less axial rigidity and relatively low levels of motor dysfunction seem to have less of a risk, independent of age.

Data regarding the neuropathological substrate(s) underlying dementia in patients with PD present a complicated story. Both the extent of AD neurofibrillary tangles and amyloid plaques tend to be increased in the brains of demented PD patients. In some situations the AD changes meet the postmortem criteria for AD and in others the changes are less severe than in AD. However, these AD changes along with the loss of subcortical neuronal systems that project to the cortex (dopaminergic, noradrenergic, serotoninergic and cholinergic) may in combination provide the neuropathological underpinnings of dementia in PD. Initially, it appeared that the expansion of the Lewy body pathology from subcortical to limbic and cortical structures might provide the neuropathological basis for dementia. The observation that Lewy body pathology expands to cortical brain regions and likely underlies PD, PD-D and DLBD with dementia further complicates understanding the nosology of these two disorders; for example, does PD transition to PD-D in some patients and DLBD in others or are PD/PD-D and DLBD separate entities? It seems most likely that the underlying substrate of PD-D is multifactorial and heterogeneous. Consistent with this notion is the recent demonstration by Compta and colleagues that a high burden of Lewy body, amyloid-β and tau are the most reliable neuropathological correlates of PD-D (Compta et al. 2011). In their study essentially all subjects who were demented had reached Braak Stages 5 and 6. α-Synuclein pathology involves diencephalic, limbic and cortical structures in Stages 4, 5 and 6 of Braak and does correlate with the clinical knowledge that dementia occurs late in the disease process. However, not all patients at Braak Stage 6 exhibit dementia. Compta's study demonstrates that Braak AD and Braak PD neuropathological criteria best correlate with and support the hypothesis that the decline in intellectual function attends the presence of α-synuclein, tau and Aβ pathologies. These observations support earlier hypotheses that α-synuclein and AD pathologies may act synergistically to initiate the pathophysiology of dementia in age-related neurodegenerative disorders (Masliah et al. 2001). Interestingly, the H1/H1 *MAPT* genotype is a very strong independent predictor of dementia in PD and the H1 haplotype is associated with elevated 4-repeat tau in Lewy body disease (Williams-Gray et al. 2009).

Therapies for PD-D are similar to those approved for AD: acetylcholinesterase inhibitors (AchE-I) and glutamate receptor antagonists. There is one well-controlled

clinical trial of PD-D treatment with rivastigmine (Emre et al. 2004) and two trials of memantine (an N-Methyl D-aspartate [NMDA]) receptor antagonist. One trial revealed improvement in the clinical global impression of change and one secondary outcome measure of improved speed on attentional tasks (Aarsland et al. 2009a). The other trial did not demonstrate efficacy (Emre et al. 2010). Since memantine is well tolerated and may have mild efficacy, it is usually started after an AchE-I. The studies with memantine are Phase II data; a comparative efficacy trial is underway. Interestingly, there is a general impression that unlike the delay in decline rate seen in AD, several AchE-I trials have also shown clinically modest but statistically significant early benefits as well. AchE-I may be more effective in treating cognitive difficulties in PD-D than in AD and may reflect the more prominent cholinergic deficit in PD.

Depression and Anxiety

Neurobehavioral features in PD include depression (mood disorders), apathy and anxiety, including panic attacks, impulse control disorders, hallucinations and delusions (Schneider et al. 2008; Aarsland et al. 2009b; Antonini et al. 2011; Blonder and Slevin 2011; Aarsland et al. 2012; Tan 2012). The prevalence of these clinical disorders in PD is substantial (up to 90 % of patients will experience one or more of these symptoms) and these difficulties are among the most common symptoms in PD that negatively affect QOL (Gallagher et al. 2010). Depression, like dementia, affects 40 % of subjects on average (prevalence data varies from 4–75 % (Schneider et al. 2008). Depressive symptoms may overlap with clinical features that are attributable to motor 'off-symptoms' (end of dopaminergic dose effectiveness) fatigue, psychomotor retardation or other non-motor symptoms including anxiety, amotivation, apathy, sleep/wake changes; thus, depression may be underestimated in PD patients. In order to improve recognition, identification and characterization of the neurobehavioral features and to delineate phenotypes working groups have reviewed aspects of depression rating scales in PD (Schrag et al. 2007), as well as the diagnostic criteria of depression in PD (Marsh et al. 2006). The important clinical points outlined by these reviews cannot be presented in detail in this chapter. The important message is that depression may be underappreciated and phenotypes not well defined; continued vigilance by clinicians is critical since altered mood and anxiety adversely affect QOL for all involved.

The spectrum of depression in PD varies from dysthymia (13 %) to depression that may be mild (10–30 %) or severe (5–20 %) (Tandberg et al. 1996; Allain et al. 2000; Reijnders et al. 2008). Depression may antedate the onset of the motor symptoms of PD. Accordingly, investigators have sought to determine whether depression is a risk factor for PD, is an early premotor sign that might predict PD or is a clinical phenotype that emerges early-initially, almost 'pari passu' in some patients. In general depression in PD may emerge a few years before diagnosis as well as during the course of the disorder. Thus, depression might sometimes serve as a premonitory event that would raise the specter of PD, especially in patients with other nonmotor symptoms. The early onset of behavioral symptoms fits within the hypothesized Braak cascade as the noradrenergic and serotoninergic brainstem nuclei

('gain setting nuclei') involved in modulating mood and behavior are involved at an earlier stage (Stage 2) than the SN (Stage 3). The pathophysiology of depression is likely multifactorial. Monoaminergic (dopamine, norepinephrine, acetylcholine) neurotransmitter systems are impaired in PD with neurodegeneration in dopaminergic mesolimbic and mesocortical neurons (dopamine neuron loss in the ventral tegmentum) and noradrenergic projection neurons (noradrenergic neuron loss in the pontine locus ceruleus) with resulting impaired monoaminergic innervation of the diencephalon, orbitofrontal and limbic cortices. Cholinergic neurons in the basal forebrain degenerate and the resulting loss of cholinergic innervation of the cortex correlates with depression (and dementia as well). Similarly, indolamine pathways are impaired as serotonergic neuronal loss occurs in the dorsal raphe nucleus in PD patients with depression and impairment of markers of 5-hydroxytryptamine (5-HT) innervation in target regions support the loss of 5-HT neurons and terminal arbors. The presence of Lewy body pathology in strategic areas of the cortex (limbic) and brainstem (locus ceruleus and SN) in PD patients appears to correlate with depression. Interestingly, recent studies of depressed elderly patients suggest that Lewy body pathology in SN and locus ceruleus underlie late life depression independent of PD (Tsopelas et al. 2011).

Anxiety occurs with and without depression in about 40 % of patients and may predate motor features of the illness. Anxiety may be quite severe, including panic attacks, or present as a generalized anxiety disorder or social phobia. Panic attacks may be experienced during 'off-times' and not specifically linked to depression. Patients become extremely frightened with the fear of immobilization. Recognition of the temporal sequence of mood-related phenomena permits proper identification of etiologies and treatment. At other times severe anxiety and panic will occur despite adequate management of the motor symptoms.

Treatment of depression and anxiety disorders in PD generally includes the use of SSRI's (serotonin specific reuptake inhibitors), despite the fact that there is almost no substantial evidence-based data to support their use. Clinical trials that have demonstrated positive results for depression in PD have been with tricyclic antidepressants (amitriptyline/nortriptyline) or dopamine agonists (pramipexole). A single controlled comparative efficacy trial in PD depression revealed superior response rates with nortriptyline (53 %) and lack of placebo superior response for paroxetine (Menza et al. 2009). However, newer SSRI's and SNRI's (serotonin and norepinephrine reuptake inhibitors) are generally used empirically since they have better side effect profiles (Aarsland et al. 2009; Weintraub and Burn 2011; Aarsland et al. 2012).

Psychosis

Psychosis is quite common in PD (Aarsland et al. 2009; Weintraub and Burn 2011). The most frequent clinical feature tends to be visual with illusions and hallucinations as well as presence and passage hallucinations. Tactile hallucinations occur as well. Auditory hallucinations are distinctly rare and should prompt consideration of other etiologies besides PD. Illusions include misperceptions of normal objects;

for example, a couch pillow may be perceived as a dog or cat, draperies as an individual standing or a bush blowing in the wind as animals moving in the yard. Hallucinations are wide ranging and are *de novo*; no objects being misperceived but are rather spontaneous events without a stimulus. Presence hallucinations, the sense someone is standing slightly behind and off to one side, and passage hallucinations, the sense that something is moving (fleeting) in the peripheral vision, are quite frequent experiences. The hallucination may become more developed if another person is seen or believed to be in the house. The person may be familiar or not, pleasant or threatening. Capgras misidentification phenomena may also occur wherein the 'spouse' is viewed as an imposter. Sometimes children in another room or a dog or cat will be seen. Patients may actually interact with the hallucination and feel comfortable in doing so, until upon approaching 'The Hallucination' it disappears. These hallucinatory events tend to occur later in the day, in low ambient light, or when an individual is not engaged. Unfortunately, the psychosis may be very disturbing as paranoid thinking evolves or threatening situations emerge. The intensity of these altered beliefs, perceptions and hallucinations are striking; their realness makes it very difficult for patients to accept that they are not real. Although the etiology of these events is not entirely clear, dopaminergic and serotoninergic degeneration and postsynaptic receptor sensitivity appear to underlie the phenomena. Generally, higher doses of carbidopa/levodopa or dopamine agonists are associated with these events and the hallucinations lessen when medications are reduced. L-DOPA replacement medication is taken up by dopamine, noradrenaline and serotonin neurons and these monoaminergic neurons all have the decarboxylase enzyme that converts DOPA to dopamine; thus, dopamine may be co-released with 5-HT and norepinephrine from their respective neurons that project widely to cortical regions, including the visual and visual-association cortices. Clozapine and quetiapine are two second generation antipsychotics that have mesolimbic selectivity of dopamine antagonism (D4 receptor), have limited antagonistic affinity for the D2 receptor and predominantly serotonin (5HT-2A) related antipsychotic effects. Both have been shown not to worsen PD motor symptoms and are commonly used to reduce psychosis. The effects of psychosis on QOL are substantial, and when paranoid and suspicious behaviors with confusion ensue, the clinical management of the psychosis requires the highest attention.

Sleep Disorders

Alterations in the sleep-wake cycle are remarkably common in PD and may not only be among the most common nonmotor symptoms in PD (80–90 % prevalence), but RBD may herald the onset of PD (Chaudhuri et al. 2010; Claassen et al. 2010). In fact RBD associated with depression/anxiety and impaired olfaction may collectively be 'clinical biomarkers' that predict the eventual development of PD (see *Biomarker* section). The range of nocturnal sleep disorders include insomnia, sleep fragmentation, vivid dreams including sleep terrors and nightmares, nocturnal movements, RBD and impaired wakefulness and hypersomnia during the day (excessive daytime sleepiness [EDS]). EDS is clinically important to recognize as patients may

experience 'sleep attacks' exacerbated by dopaminergic therapy (particularly agonists), wherein patients experience sudden onset of REM sleep and may injure themselves or others (for example, falling asleep at the wheel of a car). Disorders of sleep-wakefulness appear to reflect impairment of striatal-thalamic-cortical (frontal) neuronal circuits, although it is likely that brainstem projection systems involved in arousal and maintaining the sleep cycle are involved as well. For instance RBD and other sleep disorders may relate to degeneration of the cholinergic PPN as well as in dopamine, noradrenaline and serotonin systems.

Autonomic Disorders

The more common autonomic dysfunctions that occur in PD include cardiovascular, gastrointestinal and genitourinary dysfunction (Chaudhuri 2001; Chaudhuri et al. 2006; Pfeiffer 2007; Simuni and Sethi 2008). Orthostatic hypotension (OH) is the most frequent cardiovascular autonomic dysfunction in PD, occurring in 30–58 % of patients (Goldstein 2006) and may be present before any pharmacological treatments are initiated. Symptoms of OH are quite myriad so that OH may not be appreciated by the clinician. For example fatigue, headache, backache and 'wobbly legs' may occur with or without the more classic features of postural lightheadedness and presyncope. Over a decade ago Goldstein demonstrated that PD patients have altered sympathetic cardiac innervation by cardiac imaging with monoaminergic markers (Goldstein et al. 2000, 2002). Essentially all patients symptomatic with OH have impaired sympathetic innervation, but imaging of asymptomatic PD patients may also reveal impaired innervation. Certainly, many patients treated with dopaminergic agents will experience OH for the first time and it is likely that those with underlying autonomic dysfunction may be more likely to do so.

GI dysfunctions are major and occur oral to aboral (Pfeiffer 2003, 2011). Oropharyngeal dysphagia and esophageal motility impair swallowing and movement of food into the stomach. The frequency of these difficulties is high: 70–80 % of patients either perceive difficulties or are discovered to have such on barium swallow. Aspiration occurs in approximately 25–30 % of patients and may result in serious complications including pneumonia or choking with fatal outcomes occurring. Gastric emptying is slowed, delayed by 25–30 %, resulting in sensations of bloating and nausea as well as altered absorption of medications. For instance gastroparesis alters pharmacodynamics of absorption of L-DOPA as well as increases the length of time the medication is exposed to aromatic amino acid decarboxylase (DOPA decarboxylase [DDC]) thus, decreasing the amount of L-DOPA available for absorption. Motility in the small bowel and colon is altered with the notable observation that constipation may herald an increased risk for PD. Longitudinal aging studies in Hawaii revealed that individuals with infrequent bowel movements had a risk of developing PD that was 2.7–4.0 times greater when compared to men with two or more bowel movements per day (Abbott et al. 2001). Occasionally, severe constipation may occur with obstipation, megacolon and volvulus with secondary obstruction. Straining at stool may result in rectal prolapse and necessitate colostomy. Lastly, defecatory dysfunction may

occur throughout the course of the disease and sometimes quite early. Physiological studies have indicated a dys-synergic contraction pattern with altered coordination of contractions (abnormal phasic contractions or hypercontractile reponses) as well as dystonic contractions (Stocchi et al. 2000; Pfeiffer 2003). Recent human studies of the enteric nervous system indicate that peripheral α-synuclein pathology may be identified in the submucousal plexus of PD patients (Derkinderen et al. 2011). These studies confirm the peripheral neuropathology suggested by Braak and colleagues and provide a means by which to possibly clarify the etiology of prodromal symptoms and establish an early diagnosis. An eventual outcome might be the establishment of means by which to follow disease progression and assess interventions longitudinally.

GU disorders include bladder and sexual dysfunction and collectively may occur in up to 40–80 % of patients with PD (Winge et al. 2006; Fowler 2007; Sakakibara et al. 2008). Patients commonly experience symptoms of a hyperactive or 'irritable' bladder such as urinary frequency, nocturia and urgency with occasional urgency incontinence. Less frequently, reduced urinary stream and poor outflow control may result in incontinence. Diagnostic neuro-urological studies, including cystometry and electromyography, may be needed to fully characterize the bladder dysfunction and decide on appropriate therapy. GU dysfunction may occur early in PD, although it usually is more apparent as the disease progresses over time. Recent studies in an α-synuclein transgenic mouse model of PD revealed that GU dysfunction may occur up to six months before the onset of motor symptoms and parallel the altered bladder function in patients with synucleinopathies (e.g., hyperactive bladder dysfunction predominates with detrusor-sphincter-dyssynergia and urgency and frequent urination, including increasing nocturia, and urinary retention (Hamill et al. 2012). Human studies demonstrate a higher presence of Lewy body pathology in vesicoprostate plexi compared to other autonomic ganglia, suggesting that this transgenic model system may provide insights into neuronal vulnerability to the pathogenic process of alterations in the processing of α-synuclein (Minguez-Castellanos et al. 2007). Peripheral autonomic ganglia subserving GU functions may be among the most frequently involved structures in Stage 1 of Braak and Braak (Braak et al. 2003; Minguez-Castellanos et al. 2007). Such a model might permit examination of early interventions with disease modifying therapies. Impaired sexual function is common with up to 80 % of men and women experiencing decreased libido, as well as impaired sexual performance. Erectile dysfunction is common in men with 60–80 % experiencing difficulties; PD medications and medications for depression may aggravate an already existing problem. Erectile dysfunction is an uncommon initial manifestation and, if present, raises the diagnosis of another 'synucleinopathy', the Shy-Drager variant of MSA. Increased sexual activity or aberrant behavior (e.g., excessive pornography use) is usually secondary to treatment with dopaminergic agents, particularly dopamine agonists.

Sensory Dysfunction

Sensory abnormalities in PD are common and include altered visual, olfactory and somatosensory perceptions. Visual changes manifest as contrast sensitivity and color

discrimination; somatosensory changes range from paresthesias to pain with pain syndromes occurring in up to two-thirds of patients (Negre-Pages et al. 2008). An important sensory abnormality that may serve to identify early PD is altered olfaction. Olfactory dysfunction in PD was recognized over 30 years ago (Ansari and Johnson 1975) and the prevalence of altered olfaction approaches 90 %. Many studies have characterized deficits of identification and recognition as well as altered thresholds for detection and discrimination (Doty 2007; Boesveldt et al. 2008; Ross et al. 2008). Since changes in olfaction may occur early in PD, and in fact may precede the clinical diagnosis of PD, studies have examined whether olfactory dysfunction is a risk for developing PD in the future. Data on men in the Honolulu-Asia Aging Study revealed that impaired olfaction may predate clinical PD by at least four years (Ross et al. 2008). Studies in asymptomatic relatives of PD patients also revealed that hyposmia is associated with developing PD. Clinical deficits in olfaction appear to correlate with the neuropathological data presented by Braak and colleagues (Braak et al. 2003) that indicate the olfactory system may be one of the earliest sites of PD neuropathology with changes occurring in the anterior olfactory nucleus of the olfactory bulbs, as well as the olfactory tract and primary olfactory cortex. Curiously, not all PD patients exhibit olfactory deficits; olfaction appears to be normal in *PARK2*-related PD, but it is present in 80 % of PD patients with LRRK2 mutations. Subjects who carry the LRRK2 gene but who are asymptomatic have normal olfaction. Complicating the LRRK2 story is the fact that not all individuals with this mutation develop PD. Since olfactory changes do not appear to progress in any sequential fashion in PD, but rather are quite impaired early on, tests of smell may well be valuable as a screening tool to identify patients at risk for PD.

A brief summary of the non-motor symptoms is outlined in Table 16.1. The associated presumed neuropathological substrate and cascade as revealed by Braak and colleagues are indicated, fully realizing that these data, which are garnered from the literature, are limited and as additional data accrue, more accurate associations will be forthcoming.

16.5 Clinical Assessment Tools

PD progresses over time with a variable loss of motor function and overall disability. Various rating scales have been utilized to gauge change over time with Hoehn and Yahr (H&Y) stage, Unified Parkinson Disease Rating Scale (UPDRS) and the Schwab and England functional assessment scale being commonly applied instruments. Alves and colleagues found a mean annual decline in UPDRS and H&Y of approximately 3.0 % and the Schwab and England scores declined at 3.6 % (Alves et al. 2005). These values are slightly higher than what others have reported, but the cohorts differed to some degree and the follow up period was longer. Interestingly, neuroimaging studies have suggested that the loss of L-DOPA uptake averages a decline of 3.5 % annually. H&Y defined 5 stages (1, unilateral disease to 5, wheelchair/bed bound); patients are described as generally progressing across stages approximately every two to

three years and life expectancy might reach 18 years for patients with disease onset prior to age 50 (Hoehn and Yahr 1967). However, some patients remain at stage 1 (unilateral disease) for eight to 10 years; thus, heterogeneity in disease progression exists as well. Assessment scales remain a mainstay of monitoring the progression of the disease and currently are the major outcome measures for examining therapeutic effectiveness. Importantly, without the availability of 'biomarkers' for PD, clinical assessment tools are the benchmarks applied to determine if a therapeutic agent improves the disorder or may be identified as a disease modifying therapy.

16.5.1 Neuroimaging

Neuroimaging is not needed to make a diagnosis of PD; PD is a clinical diagnosis. Nevertheless, magnetic resonance neuroimaging (MRI) may clarify whether a patient with a primary 'Parkinsonian' disorder is more likely to have the MSA variant, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) or neurodegeneration NBIA1. The classic MRI findings in these disorders include: MSA-putaminal changes with decreased signal on T2 or slit-like hyperintensity in the lateral aspects which are seen with MSA-A & MSA-P; cerebellar and pontine atrophy with MSA-C and the 'hot-cross bun' sign in the MSA group; PSP-midbrain atrophy with 'beaking' of the rostral midbrain; CBG-contralateral cortical atrophy; NBIA1 'eye of the tiger' sign in the globus pallidus. More recently, dynamic imaging and functional imaging have provided new approaches to examining PD. A major focus of imaging efforts is to determine if imaging might provide a 'biomarker' of the illness, revealing patients at risk to develop PD (presymptomatic diagnosis) or providing a means to monitor disease progression and/or the response to disease modifying therapies. Available techniques permit the identification of changes in basal ganglia structures prior to clinical disease onset in family members at risk for PD and thus, a presymptomatic diagnostic tool is extant, although generally concentrated in research studies. The recent approval of dopamine transporter imaging with the ^{123}I-ioflupane ligand for clinical use will undoubtedly expand the information available to assist in clarifying challenging differential diagnoses.

Currently, the following imaging techniques and strategies are being actively pursued: transcranial sonography, imaging of neurochemical markers and neuronal metabolism and rather complex imaging and analyses of network function and connectivity (Eidelberg 2009; Tang et al. 2010; Stoessl 2011; Stoessl et al. 2011). A full discussion of these technologies is beyond the scope of this chapter, but a few areas deserve attention. Functional imaging utilizing positron emission tomography (PET) of the dopaminergic system permits examination of presynaptic and postsynaptic structures and estimates of functional activity. Presynaptic dopamine terminals may be estimated by examining the monoamine transporter type 2 (VMAT2), dopamine transporter (DAT) and dopamine synaptic vesicles. VMAT2 does not appear to be influenced by neuroplasticity responses and thus, is a solid marker of structure, whereas DAT and dopamine concentrations fluctuate with neuronal activity, disease

state and treatment and thus, provide approaches to functional adaptation. Postsynaptic dopamine markers include agonist and antagonist ligands for the dopamine D1 and D2 receptors. Interestingly, D1 receptor binding does not change substantially in PD, but is altered in MSA (Shinotoh et al. 1993). D2 ligands may identify postsynaptic structures, and because of varying affinities to the receptor, they provide a means to examine functional release of dopamine or adaptive responses. Strategies to examine other neurochemical markers of the cholinergic and serotoninergic systems are available as well. Metabolic studies in PD patients with markers of oxygen utilization and cerebral blood flow reveal specific alterations in various neuronal circuits as evidenced by altered synaptic activity. For instance oxygen utilization and cerebral blood flow are reduced in the supplementary motor, premotor and parietal cortices, whereas these same markers are increased in the cerebellum, pons, basal ganglia and thalamus. This pattern is consistent enough to be designated the PD-related profile (PDRP) (Eidelberg et al. 1994). This pattern is distinct from other clinically similar basal ganglia syndromes and is modifiable by therapeutic interventions and thus holds promise as a 'biomarker'. A caveat to note is the occurrence of SWEDD (Scans Without Evidence of Dopamine Denervation; patients with clinical PD but with normal scans of dopamine). However, these patients were seen early in the course of their disease and did not show PDRP on glucose PET (Eckert et al. 2007). Apparently, they may represent a variation on the theme of essential tremor (Stoessl 2011). An advance for PD will be the ability to image protein structural changes (*e.g.* α-synuclein protein and/or oligomers or Lewy bodies) in a manner similar to what has emerged for amyloid with ^{11}C-labeled Pittsburgh compound B and ^{18}F-labeled AV-45. Imaging of amyloid is relevant to the occurrence of dementia in PD since there is clear overlap of the clinical picture and neuropathology with AD. As noted previously (17.3 Pathological Features of PD) Itoyama's group has imaged *in vivo* α-synuclein deposits utilizing Carbon-11-labelled 2-[2-(2-dimethylaminothiazol-5-yl)ethenyl]-6-[2-(fluoro)ethoxy] benzoxazole (B227)]. This ligand appears to be quite lipid soluble and is able to penetrate into the brain and cells and bind intracellular synuclein fibrils and aggregates. A pilot study utilizing B227 PET in 8 patients with MSA revealed increased levels of glial cytoplasmic inclusions in the subcortical white matter, putamen, globus pallidus, posterior and anterior cingulate cortex, primary motor cortex and substantia nigra. These studies, published in 2010, suggested that *in vivo* imaging of synuclein containing glial cytoplastmic inclusions might permit distinguishing synucleinopathies from other neurodegenerative disorders, including distinguishing the MSA variants vs. PD vs. DLBD. However, to date it does not appear that this approach has reached the clinic.

It is apparent that neuroimaging, including dynamic functional imaging and network/connectivity studies, has emerged as a powerful tool to examine presymptomatic and symptomatic PD and response to treatments. By utilizing these techniques in patients with genetic or clinical syndromes that herald PD, presymptomatic diagnoses may be made. For instance, studies by Iranzo et al. (2011) indicated that 50 % of patients with the parasomnia RBD demonstrated declines in DAT binding that were of clinical significance, especially in the putamen, and that heralded the onset of disease. Three patients manifested the onset of clinical disease within

the three years of the study. Thus, improving the ability to provide *in vivo* analyses of brain structures and functions lends hope for being able to identify patients at risk, monitor therapeutic approaches and provide outcome measures of successful disease modifying/neuroprotective interventions.

16.5.2 Biomarkers

Clinical neurology in general and PD in particular would benefit from biomarkers that would clarify diagnoses, monitor the course of an illness and indicate responses to therapeutic agents designed to impede the progress or cure a given disorder. The means to measure extent of disease, remissions, relapses and cures would be major advances in patient care. As noted above, advances in brain and nervous system imaging have revealed strategies by which to identify disease patterns and monitor function and, as also indicated, have clear potential to serve as biomarkers of disease progression and response to treatment in PD. However, the costs and availability of such studies limit their usefulness. Assessment tools and clinical investigations to examine cardiovascular, gastrointestinal, genitourinary, motor, behavioral and cognitive performance, vision and olfaction exist and are actively being pursued as means to characterize disease progression and response to therapy. However, the multiple factors that influence outcome measures with these tools and the variability of responses are such that precise interpretations are not easily rendered.

As noted above, biomarkers represent indices that provide an objective assessment of a disease presence, progression and response to treatment. Genetic markers are indicators of an individual's risk for a disease and depending on the constituents of the gene, may define that a person will manifest the disease and might reflect the severity of a disorder. Genetic markers are well described in PD, but they are relevant to only a small percentage of patients. Gene markers permit identification of individuals at risk for the disease, but not all individuals carrying the 'at risk gene' will manifest the disease. Genetic markers do not provide for the monitoring of disease progression or response to treatment. Currently, for most PD patients the diagnosis, management (treatment) and longitudinal progression of the disease remain dependent on subjective evaluation of clinical function, sometimes utilizing standardized scales, but these approaches lack objectivity. Thus, the search for objective biomarkers remains a critically important area of study for PD clinical and basic neuroscientists.

Brain imaging may permit better identification of PD patients and possibly monitor disease progression; thus, neuroimaging may meet biomarker criteria and/or serve as a surrogate marker of disease progression and response to therapy (Atkinson et al. 2001). A number of current reviews summarize the range of technologies being pursued in the search for biomarkers in PD (Disease Study Group 2010; Dorsey et al. 2006, 2008; Waragai et al. 2010). The focus here will be on cerebrospinal fluid (CSF) α-synuclein and related proteins and plasma markers. As data accrue regarding these molecules, as well as others within the plasma, the usefulness of CSF and peripheral samples will be more clearly defined.

Alterations in levels of α-synuclein within the CSF may well permit a means by which to characterize synucleinopathies from other related neurodegenerative disorders that affect motoric and cognitive function (synucleinopathies vs. tauopaties) and in combination with clinical data (RBD, neuroimaging and altered olfaction) might clarify specific diagnoses in synucleinopathy and tauopathy patients with overlapping 'Parkinsonian' phenotypes (PD vs. MSA and its variants vs. PSP). Recent studies by Mollenhauer and colleagues (Mollenhauer et al. 2011) examined CSF α-synuclein and tau concentrations in patients with PD, MSA, DLB and AD and demonstrated that these two markers provide good separation of subjects with synucleinopathies from AD and other neurological disorders (PSP, normal pressure hydrocephalus). CSF α-synuclein concentrations of 1.6 pg/μL or lower showed 70.7 % sensitivity (95 % CI 65.3–76.1 %) and 52.8 % specificity (39.4–66.3 %) for the diagnosis of PD. At this cutoff the positive predictive value for any synucleinopathy was 90.7 % (95 % CI 87.3–94.2 %) and the negative predictive value was 20.4 % (13.7–27.2 %). It appears that these markers provide reasonable specificity and the positive predictive value is quite high. The authors suggest that α-synuclein concentrations in the CSF of patients presenting with synucleinopathy-type parkinsonism might be useful in stratification of patients in future clinical trials. In another study published about the same time Shi and colleagues examined seven potential biomarkers in the CSF of patients with PD (Shi et al. 2011). Total tau (t-tau), phosphorylated tau (p-tau), amyloid beta peptide (Ab1–42), Flt3 ligand, fractalkine levels, α-synuclein and DJ-1 were studied in subjects with PD, AD and MSA; the results demonstrated that PD could be culled out from normal controls as well as from patients with AD or MSA. These studies not only demonstrated remarkable sensitivity (99 %) and specificity (95 %), but CSF fractalkine/Aβ(1–42) correlated with the severity and progression of PD as well (Shi et al. 2011). These studies are important as investigation of biomarker research in PD overlaps with other neurodegenerative diseases such as AD, tauopathies, synucleinopathies, prion disorders and other neurodegenerative disorders. Since an etiopathogenic concept of 'protein seeding' and trans-synaptic progression may provide a common mechanistic platform an array of protein molecules may be required to identify useful specific and sensitive marker(s) for the family of neurodegenerative diseases. This study is a step forward in this process.

What is not clear yet is whether measures of α-synuclein or any of the aforementioned protein molecules vary during the course of the disease, whether levels might indicate various rates of progression of the disease and whether the values change with treatment. Repetitive sampling of CSF markers is not an easy matter for patients, so the practicality of serial lumbar punctures to characterize the longitudinal profile of CSF biomarkers and disease progression and response to therapy may be problematic. Levels of α-synuclein and other molecules that hold promise when sampled from the CSF do not result in similar discriminatory potential when sampled in the periphery (e.g., plasma). Thus, although plasma markers would of course be ideal, to date the data are not as promising.

Among the pathophysiological processes considered to contribute to the disease state is activation of immune mechanisms. Numerous studies have examined whether immune indices measured in plasma or CSF might serve as molecular markers of

disease risk, presence and progression (McGeer et al. 1988; Teismann et al. 2003; Michell et al. 2004; Chen et al. 2008a; Stefanova et al. 2009). A host of various molecules have been studied: IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, as well as oxidative stress related substances: reactive oxygen species, proinflammatory prostaglandins and cytokines (Brodacki et al. 2008; Waragai et al. 2010). Although studies have revealed elevated levels of various cytokines and trophic molecules in PD, these observations have yet to provide a means to segregate disease phenotypes or to monitor disease progression. Recently, studies of pentraxin 3 (PTX3) in plasma in AD, mild cognitive impairment (MCI) and PD revealed that PD patients had elevated levels of this acute phase reactive molecule and that the increases correlated with activities of daily living and the severity of motor dysfunction, but there was no correlation with neuropsychological test scores (mini-mental state exam/MMSE & clinical dementia rating/CDR; (Lee et al. 2011). Interestingly, patients with MCI and AD did not demonstrate elevated levels of PTX3. However, the data indicate that substantial overlap exists among AD and PD, with 'outliers' in both disease entities, suggesting that heterogeneity and/or subgroups might exist.

Disease heterogeneity is well known within 'idiopathic PD'; clinical and neuropathological phenotypes exist and overlap and likely reflect varying diseases etiologies, processes and neuroplasticity. It is reasonable to hypothesize that therapeutic interventions designed to slow the disease may work for one group of patients and not another. Being able to identify subgroups of patients and their response to therapies, possibly by biomarker measures, would permit targeting therapies.

Clearly, studies of biomarkers are important to pursue. The challenges that remain include identifying which markers might serve to identify presymptomatic patients (primary diagnostic markers) and which markers might adequately monitor disease progress and be responsive to interventions such that they would advance clinical trials research (surrogate end points). A validated marker or set of markers that would serve either of these measures (diagnostic or surrogate endpoint) for clinical research in PD would be a major advance in identifying and treating PD, especially if 'neuroprotective' or disease modifying therapies evolve. For instance current therapeutic trials utilize clinical endpoints that accrue over time, requiring extensive longitudinal follow-up and consuming substantial resources in order to assess the outcome of interventions. Valid biomarkers would improve the effectiveness and efficiency of all phases (Phases 1, 2, 3, 4) of clinical trials research.

16.6 Treatment

16.6.1 Symptomatic Medical Therapy

As with all neurodegenerative disorders, discussion of treatment in PD is dichotomized into two goals: symptom control and modifying the underlying disease process through neuronal protection or restoration. There remains no proven method for the latter; therefore, current therapies are all directed toward treating symptoms.

The overall goal of symptomatic therapy for motor symptoms in PD is to restore more normalized motor function and to optimally maintain performance of activities of daily living. The decision to initiate therapy remains individualized based on the patient's age, handedness, employment status, functional status, etc. Although tremor is often the symptom to bring patients to diagnosis, it is most prominent when the limb(s) are at rest and less commonly a major source of disability or reason to initiate treatment (except when socially embarrassing or with a prominent postural component). Alternatively, rigidity and akinesia/bradykinesia more often correlate with functional limitations and mobility impairment that generally prompt a decision to begin treatment.

Dopamine replacement therapies (L-DOPA and dopamine agonists) remain the mainstay of symptom control, but are not always first-line treatment. Particularly for patients who are younger and in better general health, L-DOPA administration may be delayed in an attempt to reduce long-term therapy-related motor complications (L-DOPA-induced dyskinesias, choreoathetosis and fluctuations in motor function). Early mild symptoms can be approached with a variety of different pharmacological classes with less robust clinical effects. Centrally-acting anticholinergic medications (*e.g.* trihexyphenidyl and benztropine) can be effective at reducing tremor and dystonia, but generally do not improve kinesis. Susceptibility of PD patients (specifically the elderly) to peripheral and central anticholinergic side effects (*e.g.* constipation, dry mouth, cognitive impairment) limits the general use of these agents.

Originally approved and marketed as an influenza antiviral agent, amantadine was serendipitously found to reduce all of the cardinal symptoms of PD (Schwab et al. 1969). Some years later, controlled studies confirmed modest therapeutic effects in early PD and L-DOPA-induced dyskinesia suppression in more advanced PD (Shannon et al. 1987). The mechanism of action remains uncertain, although augmentation of pre-synaptic dopamine release and NMDA glutamatergic antagonism are likely candidates. Common side effects include pedal edema and livedo reticularis (violet lace-like coloration) skin changes.

Selective irreversible MAO-B inhibitors (selegiline and rasagiline) inhibit degradation of endogenous dopamine and other catecholamines, as well as exogenously enhanced dopamine via L-DOPA. Clinically, they exert mild therapeutic effects as a monotherapy and augment L-DOPA benefits when used adjunctively. Multiple additional neuroprotective mechanisms of action have been proposed and supported in pre-clinical investigations for both, but they have yet to be definitively translated in PD (Olanow et al. 2009).

D2/3 dopamine agonists bind post-synaptic striatal dopamine receptors to alleviate parkinsonian symptoms (D3 binding is of unclear clinical significance in PD). Ropinerole (oral), pramipexole (oral) and rotigotine (transdermal) are the most widely used. Subcutaneous injectable apomorphine can be used for rapid rescue therapy in advanced disease or continuously delivered via external pump. These agents are effective at all stages of the condition (early mono- to late-adjunctive therapy), but use can be limited due to tolerability. Common adverse effects include peripheral edema, hypotension, somnolence, psychosis and impulse control disorders. Motor improvements with dopamine agonists are generally inferior

to that of L-DOPA. Preferential use of dopamine agonists (over L-DOPA) for initial dopamine replacement therapy has been associated with reduced/delayed treatment-related complications (drug-induced dyskinesia and motor fluctuations) (Rascol et al. 2000; Holloway et al. 2004).

Since the introduction of L-DOPA use in PD in the late 1960's by George Cotzias and collaborators, it has remained the gold-standard of medical therapy. This dopamine precursor is actively transported to the CNS and converted by aromatic amino acid decarboxylase (AAAD) to dopamine to increase depleted striatal dopamine concentrations and reduce parkinsonian symptoms (Cotzias et al. 1969). Improved tolerability (reduced nausea and hypotension) is achieved with simultaneous administration of peripherally acting AAAD inhibitors (carbidopa or benserazide) to reduce peripheral dopamine production. Despite the robust and consistent benefits in early disease, advanced patients often experience motor fluctuations (due to the short drug half-life), L-DOPA-induced dyskinesias and varied absorption with dose failures. A continuous intestinal delivery pump has been developed to overcome limitations related to oral delivery (Nyholm et al. 2003). Adjunctive treatment with COMT enzyme inhibitors (entacapone and tolcapone) can improve the CNS delivery of L-DOPA through inhibition of degradation to 3-O-methyldopa (3-OMD). These two agents are approved for adjunctive use with L-DOPA with entacapone being most widely used (due to rare hepatic failure associated with tolcapone) (Assal et al. 1998; Factor et al. 2001).

16.6.2 Surgical Therapy

Antedating the advent of effective pharmacological therapies, various surgical ablative techniques were developed in attempt to control PD motor symptoms. Refined stereotactic techniques allowed successful amelioration of tremor with ViM thalamotomy and cardinal symptoms of PD with pallidotomy, but limitations existed in the safety of use bilaterally (due to risk of irreversible bulbar and cognitive dysfunction). A shift in the surgical treatment paradigm began when Benabid and colleagues (Benabid et al. 1987) developed techniques for continuous high frequency stimulation of the ViM in the treatment of essential and parkinsonian tremor. During thalamic lesioning procedures stimulation below 100 Hz was found to augment and above 100 Hz was found to suppress tremor (Hassler et al. 1960; Benabid et al. 1987, 1991). Under the hypothesis that high frequency stimulation produced a lesion-like effect on target nuclei this technique was later successfully applied in PD to both the subthalamic nucleus and internal pallidum (nuclei with known increased firing rates in PD) (Pollak et al. 1993; Siegfried and Lippitz 1994). Further investigations showed improvements in off-medication UPDRS motor scores in the range of ~40–50 % (The Deep-Brain Stimulation [DBS] for Parkinson's Disease Study Group (2001)). The robust success of these new targets in controlling symptoms of advanced PD lead to generalized acceptance of DBS as a care standard for patients unable to be

managed with best medical therapy. STN has remained a favored target over GPi based on preliminary evidence suggesting superiority. Follett et al. (2010) recently reported a randomized prospective controlled trial showing favorable and similar benefits of both targets, but with greater medication reduction and more common adverse effects of depression and impaired visuomotor processing speed after subthalamic stimulation. Additional stimulation targets are newly emerging including the zona incerta for cardinal motor features and dyskinesias (Plaha et al. 2006) and the locomotion center of the PPN for freezing of gait and postural instability (Mazzone et al. 2009; Thevathasan et al. 2011).

16.6.3 Experimental Neuroprotection

Identification of therapies capable of retarding the loss of dopaminergic neurons and the other pathological changes that underpin the clinical worsening of PD remains paramount. Many encouraging pre-clinical investigations have unfortunately not translated successfully from animal model to PD. As described in this chapter, an absence of an established biomarker and reliance on clinical assessments remains a limiting factor for PD research.

Selective MAOI-Bs, selegiline and rasagiline, have extensive pre-clinical data to suggest a putative neuroprotective effect. Several mechanisms of action are proposed including: 1) Direct effects of MAO inhibition and reduced oxidative stress; 2) Independent antiapoptotic effects of propargylamines; and 3) Protective effects of aminoindans (specific to rasagiline). These mechanisms have been previously reviewed extensively (Tabakman et al. 2004; Henchcliffe et al. 2005; Chen et al. 2007). Due to the additional symptomatic benefits, confirming the disease modifying effects with clinically based primary outcome measures has proven difficult. Selegiline has been shown to reduce the development of particular symptomatology (such as freezing of gait), but remains without unequivocal evidence data to support neuroprotection in PD (Parkinson Study Group 2003; Olanow et al. 1995; Giladi et al. 2001; Palhagen et al. 2006). In a delay-start design comparative efficacy trial rasagiline showed a possible slowing of symptom progression only at the lower tested dose (Olanow et al. 2009) and the sought after indication that rasagiline demonstrated efficacy as a disease modifying therapy was not accepted by the FDA as of the Fall of 2011. As a result, the disease modifying effects remain an area of intense debate.

Abundant evidence exists that mitochondrial dysfunction and abnormalities of energy metabolism are involved in the pathogenesis of PD and other neurodegenerative disorders (Lin and Beal 2006). Creatine is a guanidine compound that serves as a spatial energy buffer between the mitochondria and cytosol to enhance energy transduction and ADP recycling and therefore, is capable of indirectly reducing oxidative stress. Several animal models of neurodegeneration have been attenuated by creatine, including MPTP neurotoxicity (Matthews et al. 1999). Creatine supplementation in *de novo* PD patients was determined to be non-futile for disease modification in

a phase II clinical trial. As a result, creatine is currently under investigation in a multi-year long-term phase III trial in symptomatically treated PD patients.

Urate is an endogenous antioxidant. Prospective epidemiological data and clinical investigations in early PD have shown that higher serum and CSF urate levels are associated with lower incidence and slower disease progression in PD, respectively (Davis et al. 1996; Schwarzschild et al. 2008; Ascherio et al. 2009). Oral administration of inosine results in elevations in systemic urate. SURE-PD is a phase II trial underway to investigate the safety and feasibility of raising serum and CSF urate with inosine in early drug-naïve PD patients.

Substantial evidence supports immune-mediated chronic inflammation as a contributor to neurodegeneration in PD. Thiazolidinediones (TZD) are a class of insulin-sensitization drugs that also act as peroxisome proliferator-activated receptor (PPAR)-γ agonists. Pre-clinical data support the hypothesis that these agents reduce reactive microglial-derived inflammation and exert a protective effect (Carta et al. 2011). Pioglitazone is a TZD currently in clinical use for treatment of Type II diabetes mellitus that is presently under phase II futility trial of disease modification in early PD.

Epidemiological data suggest that calcium channel receptor antagonist use reduces the risk of PD (Becker et al. 2008; Ritz et al. 2010). Age-related changes in intracellular calcium homeostasis with increased reliance on L-type calcium channel activity appear to increase oxidative stress on mitochondria and to reduce neuronal longevity. Isradipine is a dihydropyridine calcium channel antagonist shown to significantly reduce dopamine neuron loss associated with administration of the mitochondrial toxin MPTP in a rodent model (Chan et al. 2007, 2010). Currently in clinical use for treatment of hypertension, STRIDE-PD is a phase II clinical trial underway to investigate the disease modification potential of israpidine in early PD.

Population based studies have repeatedly shown a reduced risk of PD associated with smoking and other tobacco use, suspected to be mediated by nicotine. Multiple pre-clinical investigations have shown protective effects of nicotine on dopamine neurons in animal models of PD. Many previous investigations have yielded variable symptomatic benefits of nicotine with large double-blind trials showing no benefits. Clinical and pre-clinical studies have been extensively reviewed previously (Quik et al. 2008). The disease modifying effects and tolerability of high-dose transdermal nicotine are currently under investigation in early PD.

Several recent gene therapy efforts have been successfully advancing through early clinical development (reviewed in (Feng and Maguire-Zeiss 2010)). Two of these studies utilized adeno-associated viral vectors (AAV2) for gene transfer. CERE-120 is a modified form of neurturin (a natural homologue of glial-derived neurotrophic factor [GDNF]). Neurturin is able to improve dopamine neuron survival and promote sprouting. Although the phase II double-blind randomized trial of bilateral putaminal AAV2-neurturin injection vs. sham surgery showed no difference between groups at the intended endpoint of 12 months, a significant delayed difference of 7.6 points on the UPDRS in favor of the treated group was observed. Additional non-human primate data has suggested a lack of transfer of the neurotrophin from the putamen back

to SN dopamine neurons and the need for injection directly into this region. A further trial is underway based on this principle with an extended period of observation.

In PD the STN is disinhibited with increased activity of excitatory projections. Under this tenet enhanced local synthesis of GABA via altered gene expression may potentially normalize inhibition. A randomized double-blind phase II trial was conducted to investigate the effects of AAV2-GAD (glutamic acid decarboxylase) injected into the STN vs. sham surgery. The primary endpoint point of UPDRS change at six months showed greater reduction in the treatment group when compared to the sham group (8.1 vs. 4.7 points). Based on these positive results, further investigations are underway (LeWitt et al. 2011).

In an attempt to improve dopamine production in the striatum, intrastriatal injections of a tricistronic lentivirus encoding for tyrosine hydroxylase, aromatic amino acid decarboxylase and GTP cyclohydrolase were investigated ((Jarrya et al. 2009; Stewart et al. 2009; Grosset 2010; Stewart et al. 2011) and reviewed in (Carlsson et al. 2007; Feng and Maguire-Zeiss 2010)). A dose dependent effect has been identified with the most robust motor benefits noted to date of 43 % at six months post-injection. Further investigations with greater dose escalation are underway (Palfi, S. American Society of Gene & Cell Therapy (ASGCT) 14th Annual Meeting. Seattle, USA. 21 May 2011).

16.6.4 Potential Therapies Aimed at Protein Misfolding

Although the etiology of sporadic PD is largely unknown, the invariant loss of SNpc dopamine neurons and subsequent depletion of the neurotransmitter dopamine leads to many of the devastating clinical features of this disease. As mentioned above, the mainstay of current therapy, which is aimed at providing symptomatic relief by aiding the general slowness of movement and resting tremor, is dopamine replacement therapy. Obviously, as degeneration continues and more presynaptic striatal terminals are lost, dopamine replacement therapy becomes ineffective. As of now, there are no therapies that change the natural history of PD that is halting the progressive neurodegeneration. Gene therapeutic approaches aimed at neuroprotection and neurorestoration are under development with some currently in clinical trials (see above). This book focuses on protein misfolding disorders and therefore, in this section we are limiting our discussion to potential therapeutic approaches aimed at interfering with α-synuclein's toxic gain of function in PD (Bodner et al. 2006; Maguire-Zeiss 2008; Windisch et al. 2008; Maguire-Zeiss and Federoff 2009; Gadad et al. 2011; Hinault et al. 2011; Sultana et al. 2011).

The purported physiological and toxic functions of α-synuclein are discussed in detail elsewhere in this book (Paleologou and El-Agnaf) and are not repeated here except to emphasize that the toxic gain-of-function ascribed to α-synuclein is linked to its ability to form larger oligomeric structures. The effect of these protein structures that results in SNpc dopamine neuron vulnerability is still under investigation. Despite our lack of certainty regarding α-synuclein's mechanism of toxicity, if we

agree that oligomeric/protofibrillar forms are the most detrimental to the cell, then a therapy aimed at either preventing their formation or accelerating the accumulation of larger less toxic structures (e.g., aggregates). Recent work from El-Agnaf's group using dynamic modeling techniques suggests that intervention early in the aggregation process prior to the formation of oligomers/protofibrils (in addition to augmentation of clearance) represents the most effective therapeutic strategy (Sultana et al. 2011).

Interference with α-synuclein misfolding can theoretically be achieved using small molecule inhibitors, overexpression of interacting proteins that prevent misfolding, controlling the cellular environment that promotes protein misfolding and/or directly altering protein homeostasis. Currently there are no inhibitors of α-synuclein misfolding in clinical trials for PD, but several potentially fruitful avenues are being explored in cell and animal models of synucleinopathies. It is important to note that some small molecules that are being explored for other β-sheet containing proteins may be useful for PD, provided they are able to cross the blood brain barrier and enter cells since PD inclusions are intracellular.

Protein homeostasis is maintained by the coordinate activity of protein synthesis and degradation machinery, which encompasses the proper expression, folding, post-translational modification, targeting and ultimate disposal of the protein. Alterations in protein homeostasis has been linked to a number of neurodegenerative diseases, leading to increased efforts aimed at modulating this process (Bosco et al. 2011). Chaperone proteins play an integral part in proteostasis since they are critical for the correct folding and unfolding of proteins (Hartl et al. 2011; Walter and Ron 2011). Agents that regulate chaperone function have been shown *in vitro* and in animal models to prevent α-synuclein misfolding and subsequent cell death. A review of the role of chaperone's in the proper handling of proteins in neurodegenerative diseases is beyond the scope of this chapter but one protein, heat shock transcription factor 1 (HSF1), should be highlighted because of its integral role as a transcriptional activator of a number of chaperone proteins in response to cellular stress (*reviewed in* Neef et al. 2011). Several pharmacological activators of HSF1 are currently available (*e.g.* arimoclomol, riluzole, geldanamycin), each with different tolerability and efficacy profiles, as well as disparate mechanisms of action; however, as of yet there are no direct HSF1 activators. Neef and colleagues propose that direct activation of HSF1 would be a more focused approach decreasing the myriad of effects on cell function promoted by currently available compounds (Neef et al. 2011).

One potential method to specifically target α-synuclein misfolding within a cell would be a small molecule that binds to this protein and subsequently targets it for degradation or impairs its ability to fold into toxic oligomers. We can envision that one therapy would require two different components, one that affords the specific recognition of α-synuclein and a second that employs a targeting sequence to enhance lysosomal degradation. For example several single chain antibodies (ScFvs) have been identified that bind to human α-synuclein (Emadi et al. 2004; Zhou et al. 2004; Maguire-Zeiss et al. 2006; Emadi et al. 2007; Lynch et al. 2008). These small antigen recognition molecules have several advantages given that they are composed of the minimal antigen recognition site joined by a small linker, they can be encoded on one continuous DNA sequence allowing for both bacterial and mammalian

overexpression using common vector platforms. Another powerful advantage is that depending on the protein sorting tags added to the ScFvs, these antibodies can be produced for intracellular expression (*e.g.* intrabodies) or they can be secreted. Furthermore, intrabodies can be directed to specific organelles; for example the addition of a "KDEL" sequence would target the antigen:antibody complex to the lysosome affecting degradation (Vetrugno et al. 2005). ScFvs against α-synuclein, normal cellular prion protein and amyloid-beta have been identified and found effective in either preventing or alleviating the aggregation of their respective proteins in both animal and cell culture models (*reviewed in* Maguire-Zeiss and Federoff 2009; Messer et al. 2009; Zhou and Przedborski 2009; Maguire-Zeiss and Federoff 2010; de Marco 2011). Before ScFv therapy is tested in humans for neurodegenerative diseases many hurdles remain, including development of a robust method for long-term intracellular expression, determination of off-target effects and development of imaging methods to monitor ScFv expression in the brain. Despite these barriers, the development of an effective treatment that diminishes the amount of toxic α-synuclein conformers is likely to be transformative.

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