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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Mesencephalic and extramesencephalic dopaminergic systems in Parkinson's disease

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Abstract

Neurodegeneration of the nigrostriatal dopaminergic system and concurrent dopamine (DA) deficiency in the basal ganglia represent core features of Parkinson's disease (PD). Despite the central role of DA in the pathogenesis of PD, dopaminergic systems outside of the midbrain have not been systematically investigated for Lewy body pathology or neurodegeneration. Dopaminergic neurons show a surprisingly rich neurobiological diversity, suggesting that there is not one general type of dopaminergic neuron, but rather a spectrum of different dopaminergic phenotypes. This heterogeneity on the cellular level could account for the observed differences in susceptibility of the dopaminergic systems to the PD disease process. In this review, we will summarize the long history from the first description of PD to the rationally derived DA replacement therapy, describe the basal neuroanatomical and neuropathological features of the different dopaminergic systems in health and PD, explore how neuroimaging techniques broadened our view of the dysfunctional dopaminergic systems in PD and discuss how dopaminergic replacement therapy ameliorates the classical motor symptoms but simultaneously induces a new set of hyperdopaminergic symptoms.

Keywords Parkinson disease · Dopamine · Dopaminergic systems · Motor symptoms · Dopaminergic therapy · L-DOPA

Abbreviations

^{123}I-IBZM	^{123}I-iodobenzamide
^{18}F-FDG	^{18}F-fluorodeoxyglucose
AADC	Aromatic L-amino acid decarboxylase
DA	Dopamine
DAT	Dopamine transporter
ICD	Impulse control disorder
LB	Lewy body
LID	L-DOPA-induced dyskinesia
LN	Lewy neurite
MCI	Mild cognitive impairment
MSA	Multiple system atrophy
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PSP	Progressive supranuclear palsy
RBD	REM sleep behavior disorder
RRF	Retrorubral field
SN	Substantia nigra
STR	Striatum
TH	Tyrosine hydroxylase
UPDRS	Unified Parkinson's Disease Rating Scale
VMAT2	Vesicular monoamine transporter 2
VTA	Ventral tegmental area

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Introduction

The basic clinical symptomatology of Parkinson's disease (PD) has been well known for 200 years and has been expanded ever since. But how can we identify the neuropathological correlates of these symptoms? How can we link symptoms to certain brain circuit dysfunction, or vice versa, how can we predict the clinical manifestation of a dysfunctional system? The comprehension of the association of neuronal systems and physiological functions/dysfunctions is crucial for the rational development of therapy to alleviate disabling symptoms. To investigate the link between symptomatology and neuropathology in humans, we consider the following: (1) post-mortem neuropathological studies to explore neurodegeneration, distribution of Lewy bodies/neurites (LB, LN) and biochemical alterations; (2)

neuroimaging studies in combination with radiotracers to examine dysfunctional neurotransmission; and (3) clinical studies investigating the potential of certain medications to alleviate, worsen or even provoke certain symptoms.

In this review, we will briefly summarize the long road to the discovery of a dysfunctional dopaminergic system in PD laying the ground for the still up-to-date gold standard of therapy and then focus on the emerging evidence of the dysfunctional dopaminergic systems of the brain in PD.

A long road to go

The first medical description of PD dates back to 1817 when James Parkinson published his monograph entitled 'An Essay on the Shaking Palsy' based on the depiction of the clinical picture of six patients (Fig. 1) (Parkinson 1817). Fifty-five years later, in 1872, Jean-Martin Charcot identified bradykinesia as a defining feature of PD and suggested that tremor is not an obligate symptom of the disease. He therefore proposed the term "Parkinson's disease", thereby arguing against the term 'shaking palsy'. At this time, neuropathological correlate(s) of the diverse symptoms had not been resolved and PD remained a highly debilitating disorder without effective treatment.

Almost 100 years after the first description, neuropathological studies brought a first breakthrough in PD linking degeneration of the substantia nigra (SN) to the characteristic parkinsonian motor symptoms. In 1893, Georges Marinesco and Paul Blocq were the first to suggest that a lesion of the midbrain could contribute to the motor symptoms seen in PD. Their hypothesis was based on an autopsy of a patient with unilateral parkinsonism, which revealed a tuberculous nodule confined to the right cerebral peduncle. Two years later, Edouard Brissaud hypothesized that the SN might be the major pathological site of PD. This hypothesis was validated by the pioneering work of Constantin Trétiakoff in 1919, who demonstrated substantial loss of pigmented nigral cells in post-mortem PD brains and inclusion bodies in the remaining neurons which he called 'corps de Lewy' (Lewy body, LB), in honor of their first describer Friederich H. Lewy (Trétiakoff 1919). The neurochemical consequences of SN degeneration, that is, dopamine (DA) deficiency in the basal ganglia of PD patients, however, remained unknown until 1960.

Thus, almost 40 years later, in 1957, Arvid Carlsson demonstrated in a pioneering work that administration of reserpine led to depletion of brain DA levels and onset of motor deficits in animals mimicking the symptomatology of parkinsonism. He also proved that application of L-DOPA, a blood–brain barrier-passing precursor of DA, and noradrenaline could alleviate these symptoms by restoring the brain DA to normal levels (Carlsson 1959; Carlsson et al. 1957). This work built the basis for the DA era of PD and was later honored with the Nobel Prize for medicine. Soon after this, Oleh Hornykiewicz and Herbert Ehringer demonstrated that

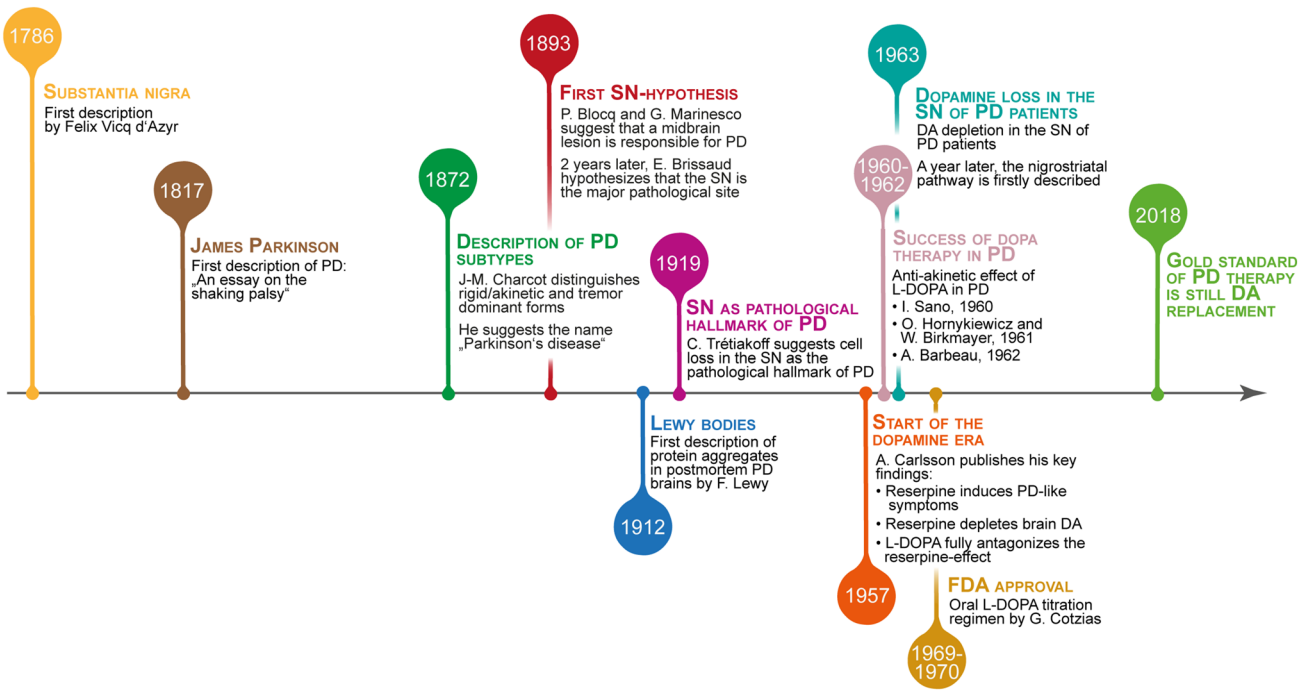

Fig. 1 Milestones of PD pathogenesis and therapy

DA is depleted in the putamen, caudate nucleus and SN of post-mortem brains of Parkinson patients (Hornykiewicz 1963; Ehringer and Hornykiewicz 1960). Subsequently, they intravenously administered L-DOPA to volunteering patients. The effect of this therapy was the complete abolishment of the akinesia (Birkmayer and Hornykiewicz 1961). Thus, they introduced L-DOPA to the field of neurology as the first rationally developed therapy of PD. In 1970, based on the elaborate work of George C. Cotzias (Cotzias et al. 1969), the US Food and Drug Administration (FDA) finally approved L-DOPA as the first drug to treat PD.

Although we know for a long time that the dopaminergic system of the brain is neither among the first regions affected in the course of the disease, nor is it solely accountable for the wide spectrum of symptoms, the gold standard of therapy is still based on the restoration of dopaminergic neurotransmission by means of administration of L-DOPA or DA receptor agonists (Oertel 2017).

Parkinsonism as the core feature of PD

PD is a clinical diagnosis based on the occurrence of the characteristic parkinsonian motor abnormalities plus at least two supportive criteria and the complete absence of absolute exclusion criteria and red flags (Table 1) (Postuma et al. 2015). The three cardinal motor features of PD are bradykinesia/hypokinesia, tremor and rigidity. Typically, PD patients initially present with unilateral motor signs, most commonly with akinesia in combination with resting tremor affecting one of the upper extremities (Pallone 2007). The motor symptoms then gradually spread to the contralateral and lower limbs, but the initial asymmetry remains (Weintraub et al. 2008; Rodriguez-Oroz et al. 2009).

Table 1 Diagnostic criteria for PD (modified from Postuma et al. 2015)

Diagnostic criteria for PD
Step 1. Diagnosis of parkinsonism
Bradykinesia/hypokinesia + one of the following
Resting tremor
Rigidity
Step 2. Supportive criteria
At least 2 out of 4
Clear and dramatic response (> 30% in UPDRS III score) to dopaminergic therapy
L-DOPA-induced dyskinesia
Resting tremor of a limb
Positive test of either olfactory dysfunction or cardiac sympathetic denervation (scintigraphy)
Step 3. Absence of absolute exclusion criteria
Step 4. Absence of red flags

Bradykinesia means slowness of movement, whereas hypo-/akinesia is defined as reduced or diminished amplitude and frequency of spontaneous movements (Rodriguez-Oroz et al. 2009). Patients often describe this as 'weakening of the limb', but upon examination, the muscle strength is not altered. Bradykinesia usually presents as a slowness in everyday routine activities and reduced unilaterally arm swing during walking (Lewek et al. 2010; Jankovic 2008). Other signs of this symptom can be a decreased blinking rate (Biousse et al. 2004; Karson 1983), reduced facial expressions (hypomimia) and gesturing, micrographia and a monotone soft speech (hypophonia) (Ho et al. 1999).

Resting tremor (4–6 Hz), representing the most obvious and therefore stigmatizing symptom of PD, is defined as an involuntary rhythmic movement of a body part, which affects usually one of the upper extremities in the early phase of the disease (Jankovic 2008). Tremor is commonly one of the first motor signs to appear and starts generally in the fingers or the thumb, resulting in the typical "pill-rolling tremor" (Kalia and Lang 2015). It becomes apparent during resting state, weakens or even disappears during voluntary movement of the limb and worsens when the patient is stressed or anxious.

Rigidity refers to an increased muscle tone in both the agonist and antagonist muscles resulting in stiffness of the limb. Upon clinical examination, a resistance to passive movement in the extremity can be observed. The resistance may be either smooth (lead-pipe phenomenon) or fluctuating (cogwheel rigidity) (Weintraub et al. 2008), the latter rather representing a mixture of tremor and rigidity.

As the disease advances, postural instability becomes progressively apparent, representing the most common cause of falls and significantly decreasing the quality of life (Williams et al. 2006; Koller et al. 1989; Michalowska et al. 2005). Although postural instability usually develops during the course of the disease, it is mostly not present in early PD and an early occurrence therefore suggests an alternative diagnosis (Jankovic 2008; Postuma et al. 2015). The combination of cardinal motor symptoms, impairment of balance and an anterior shift of the mean center of gravity position finally results in the fully evolved late-stage parkinsonian posture and gait: the patient bends forward into a flexed truncal position and the stride length and walking pace substantially decrease. The patient begins to shuffle and may scrape the foot on the floor with reduced or absent arm swing (Morris et al. 1994; Jankovic 2008; Ebersbach et al. 2013; Błaszczyk et al. 2007).

Apart from these motor symptoms, several non-motor features occur in PD, with a substantial impact on the quality of life of patients (Schrag 2000). The most prevalent non-motor features are the following: reduced gastric and bowel motility resulting in constipation, olfactory dysfunction, sleep disturbances [e.g., REM sleep behavior disorder

(RBD)], forgetfulness (cognitive decline), depression, apathy and symptoms of autonomic dysfunction (e.g., urinary urgency, dysfunctional thermoregulation, sweating, orthostatic hypotension, erectile dysfunction) (Martinez-Martin et al. 2007). Importantly, non-motor features often precede the motor symptoms and therefore the diagnosis of PD by decades (Siderowf and Lang 2012).

In contrast to the well-known symptomatology of PD, it has been increasingly difficult to identify the neurobiological correlates underlying the parkinsonian symptoms and integrate them in a pathophysiological model that explains the origin of brady-/akinesia, tremor and rigidity. While striatal DA deficiency could be clearly linked to the onset of motor dysfunction, the wide spectrum of symptoms and compensatory mechanisms in PD cannot be attributed solely to the loss of DA.

The dopaminergic systems of the brain

To understand the link between symptoms and a dysfunctional neuronal brain circuit, it is essential to explore the neurotransmitter system and its physiological functions. Therefore, we will briefly summarize the dopaminergic systems of the brain and their implications in distinct physiological functions.

The dopaminergic neurons of the mammalian central nervous system are distributed along ten distinct neuronal populations located in the ventral mesencephalon (A8–A10), diencephalon (A11–A15), olfactory bulb (A16) and retina (A17) (Fig. 2) (Björklund and Hökfelt 1984; Björklund and Dunnett 2007; Dahlstroem and Fuxe 1964). All of these different subsystems are engaged in several biological functions such as motor, sensory and autonomic control, reward mechanisms and cognition (Smeets and González 2000; Montague et al. 2004).

The neurons of the ventral mesencephalic dopaminergic complex (A8–A10) are morphologically indistinguishable and rather form a continuum without clear anatomical boundaries. The A8 cell group is primarily located in the retrorubral field (RRF), whereas A9 neurons are found in the SN pars compacta, and A10 refers to dopaminergic neurons within the ventral tegmental area (VTA) (Vogt Weisenhorn et al. 2016; Yetnikoff et al. 2014). All of them form one extensive mesotelencephalic dopaminergic projection system comprising three major pathways: (1) a ventral mesostriatal or mesolimbic system which is involved in motivated behaviors predominantly originating in the VTA (A10); (2) a mesolimbocortical or mesocortical system responsible for memory and learning, mainly originating in the VTA (A10); and (3) a dorsal mesostriatal or nigrostriatal pathway, which is engaged in voluntary motor control mainly originating in the SN pars compacta (A9) (Figs. 3, 4) (Björklund and Dunnett 2007; Zeiss 2005; Flückiger et al. 1985).

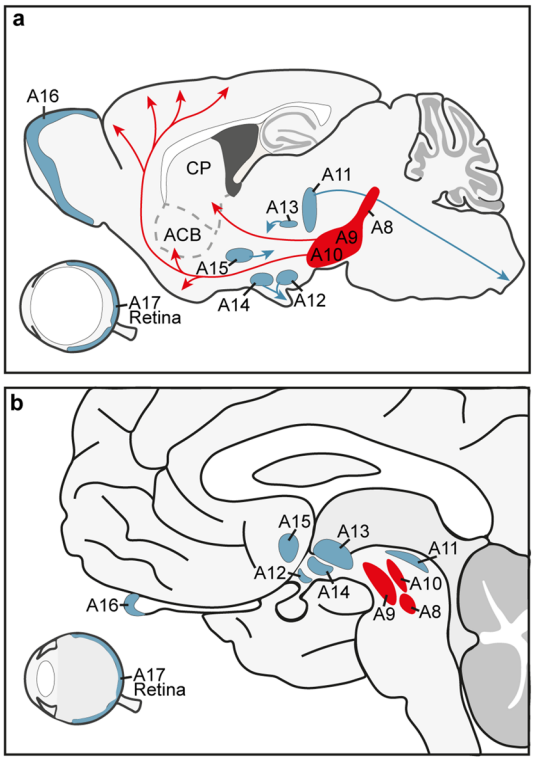

Fig. 2 Localization and PD pathology of the dopaminergic systems in mice (**a**) and humans (**b**). The color of the different nuclei refers to the presence or absence of pathology seen in PD. Green—not affected, red—affected, blue—not sufficient data available. **a** Modified from Björklund and Dunnett (2007)

The diencephalic dopaminergic system (A11–A15) contains five distinct cell groups. The neurons of A11 are located in the periventricular gray of the caudal hypothalamus and thalamus and project mainly to the dorsal horn of the spinal cord giving rise to the diencephalospinal pathway (Flückiger et al. 1985; Watson et al. 2012). It was suggested that these neurons contribute to anti-nociception and motor and autonomic reflexes (Clemens and Hochman 2004; Lindvall et al. 1983; Fleetwood-Walker et al. 1988). The tuberoinfundibular dopaminergic neurons of the arcuate nucleus (A12) and the dopaminergic neurons of the preoptic area (A14) are engaged in neuroendocrine functions by secreting DA to the hypophyseal portal blood system, thereby regulating prolactin (PRL) and growth hormone (GH) secretion (Ben-Jonathan and Hnasko 2001; Turiault et al. 2007). The A13 dopaminergic cell group is located within the medial part of the zona incerta and projects locally into the hypothalamus forming the incertohypothalamic pathway (Flückiger et al. 1985). This subsystem is engaged in the regulation of gonadotropin-releasing hormone (GnRH) secretion (Turiault et al. 2007). The neurons of the A15 cell group

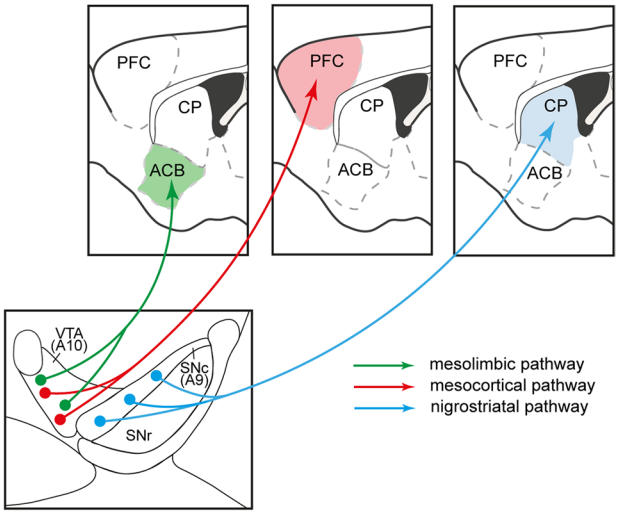

Fig. 3 Mesotelencephalic pathways. The A8–A10 dopaminergic cell groups are found in the ventral midbrain. They form one extensive mesotelencephalic pathway comprising three major pathways: (1) mesolimbic pathway projecting mainly from the VTA to the ventral STR; (2) mesocortical pathway mainly originating in the VTA and projecting to the prefrontal cortex (PFC); and (3) nigrostriatal pathway originating in the substantia nigra and projecting to the dorsal STR. *ACB* nucleus accumbens, *CP* caudoputamen, *VTA* ventral tegmental area, *SNr* substantia nigra pars reticulata; *SNc* substantia nigra pars compacta

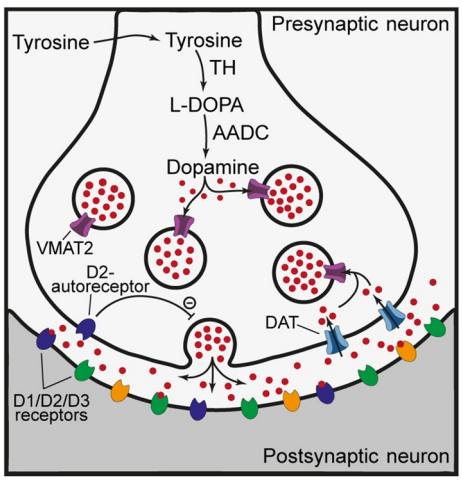

Fig. 4 A traditional dopaminergic neuron. *TH* tyrosine hydroxylase, *AADC* aromatic acid decarboxylase, *VMAT2* vesicular monoamine transporter 2, *DAT* dopamine transporter. Modified from (Oertel 2017)

are located in the rostral hypothalamic periventricular area. Their function is not yet fully understood, but they seem to be involved in the regulation of GnRH as well (Brown et al. 2015; Clarkson and Herbison 2011).

The A16 dopaminergic cells of the olfactory bulb are interneurons found in the periglomerular layer (Halász et al. 1981) and play a pivotal role in odor discrimination and odor processing (Wilson and Sullivan 1995; Tillerson et al. 2006; Taylor et al. 2009). The retinal dopaminergic cells (A17) are neurons of the amacrine subtype found in the inner nuclear and inner plexiform layers of the retina (Archibald et al. 2009). Retinal dopaminergic neurotransmission plays a central role for contrast sensitivity, visual acuity and retinal light adaption by induction of the transition from the rod circuit (dark-adapted state) to the cone circuit (light-adapted state) (Archibald et al. 2009; Jackson et al. 2012; Korshunov et al. 2017; Ribelayga et al. 2008).

What are the prerequisite features a neuron has to possess to be considered dopaminergic? The classical dopaminergic neuron is defined by the presence of: (1) DA, (2) DA-synthetizing enzymes [i.e., tyrosine hydroxylase (TH) and aromatic L-amino acid decarboxylase (AADC)], (3) DA-degrading enzymes (i.e., monoamino oxidases), (4) DA transporters [i.e., vesicular monoamine transporter 2 (VMAT2), DA transporter (DAT)] and (5) autoreceptors (i.e., D_2 receptor) (Vernier et al. 2004). Simultaneously, dopaminergic neurons lack dopamine-β-hydoxylase and phenylethyl-*N*-methyl transferase, the two enzymes required for the conversion of DA into noradrenaline and subsequently adrenaline (Vernier et al. 2004). Importantly, not all of the above-mentioned neuronal populations (A8–A17) contain the complete set of proteins involved in dopaminergic neurotransmission, that is, some cell groups only partially fulfill all of the criteria of a traditional dopaminergic phenotype. For example, in the non-human primate, the A11 neurons contain TH, but at the same time lack detectable levels of AADC or DAT, suggesting that these neurons are L-DOPAergic, rather than dopaminergic (Barraud et al. 2010). Among all dopaminergic cell groups, the A8 (RRF), A9 (SN pars compacta) and A10 (VTA) neurons exhibit the most complete dopaminergic phenotype (Vernier et al. 2004). The above introduced traditional map of the brain's dopaminergic system was generated based on detecting DA complemented with visualizing the distribution of TH immunoreactivity (Björklund and Dunnett 2007, Björklund and Hökfelt 1984; Dahlstroem and Fuxe 1964). As a consequence, the map does not reflect the diversity of the different dopaminergic subsystems. The heterogeneity furthermore suggests that there is not one general type of dopaminergic neurons, but rather a spectrum of different dopaminergic phenotypes.

Neuropathological alterations of the dopaminergic systems in PD

Neuropathological studies, given their cross-sectional nature, allow the investigation of the spatial pattern of pathology, i.e., the aspects of the localization of LB pathology, neurodegeneration and consequent biochemical

alterations. The advantages of neuropathological studies are: (1) high resolution in space which enables the detection of pathology at single-cell level and (2) the detection of LB/LN pathology distribution, which is currently not possible with in vivo neuroimaging studies, due to the lack of an α-synuclein radiotracer.

Although it is commonly accepted that a dysfunctional dopaminergic neurotransmission is one of the core features of PD, and that the dopaminergic systems of the brain are heterogeneous and therefore may have different susceptibility to neurodegenerative processes, the dopaminergic neuronal populations outside the midbrain have not been systematically investigated in PD.

Since the discovery of DA depletion in the SN and striatum (STR) of Parkinson patients (Hornykiewicz 1963), several neuropathological studies were conducted to estimate dopaminergic neurodegeneration of the SN pars compacta. The average loss of pigmented nigral neurons compared to age-matched healthy controls ranges between 41 and 79% across studies, on average 67% (Javoy-Agid et al. 1984; Bogerts et al. 1983; Waters et al. 1988; Hirsch et al. 1988; German et al. 1989; Alberico et al. 2015; Zarow et al. 2003; Damier et al. 1999; Gibb and Lees 1991; Kempster et al. 1989; Halliday et al. 1996). Interestingly, the neuropathological process does not homogeneously affect the full extent of the dopaminergic SN. A characteristic topology of neurodegeneration can be observed: neurons of the ventrolateral and caudal subregion, called ventral tier, are primarily affected (around 70–90% cell loss), whereas neurons in the dorsal tier are relatively resistant to the degenerative process (25–70% cell loss) (Damier et al. 1999; Fearnley and Lees 1991; Halliday et al. 1996; Hirsch et al. 1997). In consensus with these findings is the uneven pattern of DA depletion in the STR. The putamen, mostly receiving input from the ventral tier of the SN, shows almost complete DA depletion (< 1% of DA remaining), whereas the caudate nucleus has still substantial levels of DA (~ 40% of DA remaining) (Fig. 6b) (Kish et al. 1988; Waters et al. 1988; Fahn et al. 1971). One study showed that the cell loss of pigmented, neuromelanin-containing SN neurons is less than the loss of TH-positive cells at all studied time points, indicating that prior to cell death, dopaminergic neurons become dysfunctional and decrease their dopaminergic phenotypic expression (ghost cells) (Kordower et al. 2013). This suggests that at the time of the manifestation of the cardinal motor symptoms, symptoms most likely occur due to nigrostriatal dysfunction rather than frank neurodegeneration (Kordower et al. 2013). Besides neurodegeneration, the SN pars compacta also exhibits severe LB and LN pathology (Braak et al. 2003; Gibb and Lees 1989; Seidel et al. 2015). In fact, a combination of nigral Lewy pathology and neurodegeneration of the dopaminergic SN is highly specific for PD and even a prerequisite for the definite neuropathological diagnosis (Gelb et al. 1999; Dickson et al. 2009).

The A8 dopaminergic neurons of the RRF show minor or no degenerative changes in PD (McRitchie et al. 1997), whereas the dopaminergic neurons of the VTA (A10) show abundant LB/LN pathology (Seidel et al. 2015) and substantial neurodegeneration in PD. The reported cell loss of neuromelanin-pigmented VTA neurons in PD ranges between

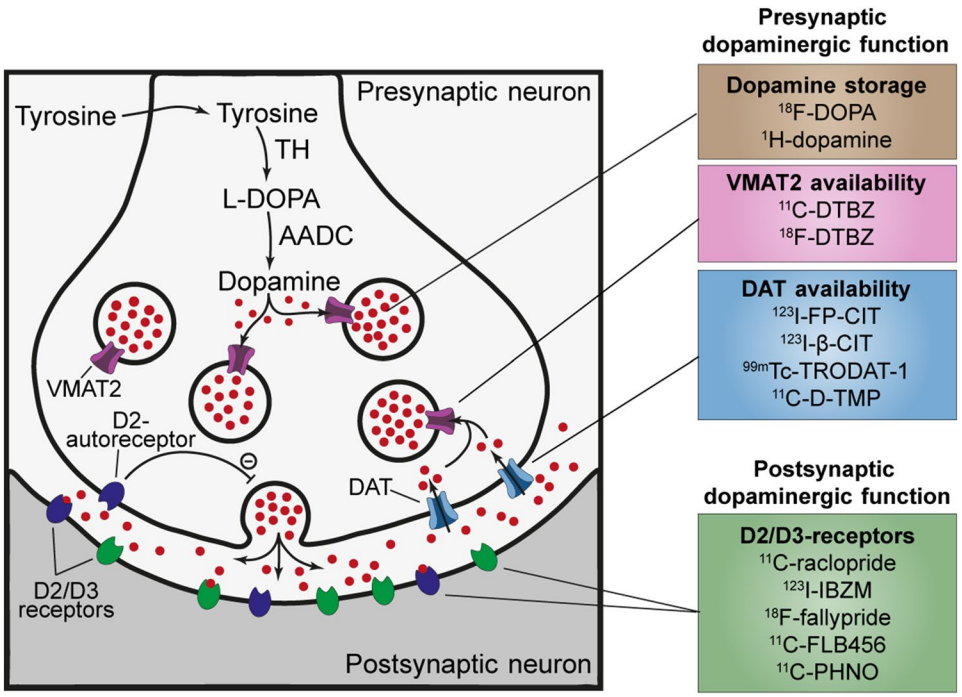

Fig. 5 Available radiotracers for in vivo imaging of the dopaminergic systems. Radiotracers can be used to image the presynaptic dopaminergic activity (DA storage, VMAT2 and DAT availability) or the postsynaptic dopaminergic function (D2/D3 receptors) with PET and SPECT approaches

40 and 77%, on average 53% (Hirsch et al. 1988; German et al. 1989; Alberico et al. 2015; Javoy-Agid et al. 1984; Bogerts et al. 1983; Uhl et al. 1985; Waters et al. 1988; Damier et al. 1999; McRitchie et al. 1997; Javoy-Agid and Agid 1980). A direct comparison of the VTA and SN cell counts is—due to the different samples and statistical methods—difficult. Only a few studies have directly compared nigral and ventral tegmental neuromelanized cell counts by investigating the same midbrain tissue samples. According to their results, the degree of neurodegeneration in the SN usually exceeds that of the VTA by 20% on average (Damier et al. 1999; German et al. 1989; Hirsch et al. 1988). This suggests that, although these two cell populations have a lot of common traits, certain factors partially decrease the susceptibility of VTA (A10) neurons to neurodegeneration and/or increase the vulnerability of SN (A9) neurons.

The diencephalic dopaminergic neuronal populations (A11–A15) have not attracted much attention in PD yet, although their possible involvement in the disease process might contribute to certain autonomic and neuroendocrine dysfunctions seen in PD patients (Politis et al. 2008; Chaudhuri and Schapira 2009). It is reported that virtually all nuclei of the hypothalamus exhibit LB pathology to some extent after a certain disease duration (Langston and Forno 1978). The most severely affected hypothalamic regions are the tuberomammillary nucleus and the lateral and posterior hypothalamic nuclei, regions that do not contain dopaminergic cell groups (Langston and Forno 1978; Braak et al. 2003, 2004). Interestingly, the tuberoinfundibular region which exhibits the highest density of hypothalamic dopaminergic neurons (A12) is relatively spared of LB pathology (Langston and Forno 1978). Nevertheless, to date no study which investigated LB formation specifically in hypothalamic dopaminergic cells exists. In addition, studies on hypothalamic dopaminergic neurodegeneration are also sparse. Only one study aimed to quantify pigmented neuronal cell counts in hypothalamic nuclei of PD patients. Interestingly, no significant cell loss was detected (Matzuk and Saper 1985). Taken together, studies of the hypothalamic dopaminergic system in PD are sparse and their results are controversial.

The olfactory bulb is one of the first brain regions affected during PD (Braak et al. 2003) and hyposmia is present in up to 90% of PD patients (Doty et al. 1988; Haehner et al. 2011), often preceding the classical motor symptoms by more than a decade (Kalia and Lang 2015). Several studies detected dense accumulation of LBs in granule, mitral and tufted cells and the anterior olfactory nucleus (Ubeda-Bañon et al. 2010; Sengoku et al. 2008; Braak et al. 2004). Interestingly, the periglomerular layer, in which the dopaminergic A16 neurons are localized, is relatively spared of the α-synucleinopathy and LBs only occasionally co-localize with TH immunoreactivity (Ubeda-Bañon et al. 2010; Sengoku et al. 2008; Cave et al. 2016). Studies estimating the number of bulbar dopaminergic neurons are contentious. Two independent studies reported that TH-positive neuronal count was doubled in the olfactory bulbs of PD patients compared to healthy controls (Huisman et al. 2004; Mundiñano et al. 2011), while other studies revealed no significant difference between PD and healthy controls (Cave et al. 2016; Ubeda-Bañon et al. 2010; Huisman et al. 2008). Taken together, dopaminergic cells of the olfactory bulb are spared of the α-synucleinopathy. However, whether their neuronal numbers increase during the disease duration and whether this change arises as a consequence of the disease process or DA replacement therapy needs to be further investigated.

Data on the retinal dopaminergic system (A17) in PD are sparse. A very recently published study was the first one to examine and describe phosphorylated α-synuclein-positive, LB- and LN-like inclusions in the retina of PD patients (Ortuño-Lizarán et al. 2018). Morphological changes were exclusively found in the ganglion cell layer and exclusively co-localized with ganglionic cell markers, thereby excluding the possibility of LB formation in dopaminergic amacrine cells. However, despite the lack of α-synucleinopathy in retinal dopaminergic cells, neurochemical evidence of a dysfunctional retinal DA neurotransmission exists. Retinal dopaminergic cells of PD patients show decreased TH immunoreactivity (Nguyen-Legros 1988), and simultaneously significantly lower levels of retinal DA were measured (Harnois and Di Paolo 1990).

It has been hypothesized for a long time that a dysfunctional DA homeostasis might contribute to the selective vulnerability of catecholaminergic neurons in PD (Lotharius 2002; Lohr et al. 2014; Pifl et al. 2014; Uhl 1998; Caudle et al. 2007; Post et al. 2018; Segura-Aguilar et al. 2014; Gandhi et al. 2012; Bayersdorfer et al. 2010; Surmeier 2018; Surmeier et al. 2017). Moreover, DA seems to promote the formation and secretion of SDS-resistant α-synuclein oligomers, thereby eventually contributing to the initiation and progression of the disease (Lee et al. 2011). Despite this central role of DA, extramesencephalic dopaminergic systems have not been systematically investigated for α-synucleinopathy and/or neurodegeneration. Substantial literature exists on the ventral mesencephalic dopaminergic (A8–A10) nuclei considering their involvement in the disease process. These comparative data allow to clearly recognize a spectrum of susceptibility, in which the nigral dopaminergic cells of the ventral tier (A9) are the most vulnerable, followed by the VTA (A10), the dorsal tier of the SN (A9) and the RRF (A8). Identifying the factors which render certain neurons particularly vulnerable or resistant to the disease process remains a key challenge. It has been suggested that the different protein expression patterns and thus the interaction of various proteins influence the

susceptibility of these neuronal populations (Double et al. 2010). Specific proteins and protein expression patterns (proteomes) which could account for the observed spectrum of vulnerability within the mesencephalic dopaminergic cell populations have been found. These are of interest for cellular metabolism and also for the electrophysiological firing patterns of these cell groups. Whereas the pacemaking of the less vulnerable VTA neurons relies on voltage-dependent Na^+ channels (Puopolo et al. 2007), adult nigral neurons use L-type voltage-gated Ca^{2+} channels of the $Ca_v1.3$ subtype to maintain autonomous pacemaking, leading to sustained Ca^{2+} influx to the cytosol (Chan et al. 2007; Nedergaard et al. 1993). In the most vulnerable ventral tier of the SN, the latter is combined with a substantially lower intracellular Ca^{2+} buffering capacity, due to the absence of calbindin and significantly lower expression levels of parvalbumin and calretinin compared to the dorsal tier of the SN or the VTA, respectively (Chung et al. 2005; Yamada et al. 1990; Parent et al. 1996; McRitchie et al. 1996). As a consequence, these neurons have a high intracellular Ca^{2+} burden leading to high energy demands due to ATP-dependent Ca^{2+} extrusion mechanisms (Surmeier et al. 2011; Chan et al. 2010). Furthermore, metabolic studies have shown that nigral neurons have an almost threefold higher basal oxidative phosphorylation rate than VTA neurons and thus a substantially elevated basal oxidative stress level and a significantly lower reserve respiratory capacity (Pacelli et al. 2015). This means that nigral neurons are less capable of increasing their ATP production when higher energy demands occur. For thourough reviews on additional potential vulnerability factors, see Double et al. (2010) and Brichta and Greengard (2014).

What we can learn from neuroimaging studies

Neuroimaging studies have become increasingly valuable tools to link pathological alterations with motor and nonmotor symptoms, investigate etiology and pathomechanisms, monitor disease progression, support differential diagnosis of parkinsonism and assess the outcome of therapeutic approaches (Politis 2014). In this review, we will focus on three major applications which are relevant regarding dopaminergic dysfunction in PD: (1) the variety of imaging agents allows us to investigate the changes in the dopaminergic systems and metabolic activity caused by PD and thereby broadens our understanding of the molecular and cellular disease pathogenesis and progression (Weingarten et al. 2015; Politis 2014); (2) PET-, SPECT- and MRI-based imaging can be used in the clinical setting to assist in the differential diagnosis of idiopathic PD vs. atypical parkinsonian syndromes or other causes of parkinsonism (Kägi et al. 2010; Scherfler et al. 2007); (3) neuroimaging studies can be used to detect subclinical levels of dopaminergic dysfunction and thus facilitate the identification and risk stratification of prodromal PD patients (Meles et al. 2017; Heller et al. 2017). Apart from these indications, functional neuroimaging has various other applicabilities, such as assessing the therapeutic effect of deep brain stimulation or embryonic cell transplantation (Weingarten et al. 2015; Natale et al. 2018).

A general advantage of functional neuroimaging studies is their potential to assess in vivo dysfunction of neuronal circuits, i.e., how the affected neurons behave in their neuronal network once they have reached a dysfunctional state. Additionally, they enable the analysis of the spatiotemporal pattern of neuropathology, that is, the progression of cellular and regional dysfunction in space and time. Dopaminergic dysfunction has been one of the major interests over the past 30 years of imaging in PD. The development of different imaging agents and tracers enabled the assessment of presynaptic dopaminergic dysfunction and postsynaptic DA receptor changes (Fig. 5). As expected, the ventral midbrain (A8–A10) of PD patients exhibits a reduction of presynaptic dopaminergic tracer uptake indicating dopaminergic degeneration (Joutsa et al. 2015; Goldstein et al. 2008; Ito et al. 2002; Hsiao et al. 2014). As a consequence, brain regions receiving dopaminergic input from A8–A10, namely the putamen, caudate nucleus and ventral STR (nucleus accumbens and olfactory tubercle), show reduced tracer binding reflecting dopaminergic denervation (Pavese et al. 2011; Joutsa et al. 2015; Lewis et al. 2012; Hsiao et al. 2014). It could be shown that the loss of tracer binding is uneven between the subregions of the STR: the dorsal putamen displays the most severe reduction, followed by the caudate nucleus and the ventral STR (Bohnen et al. 2011; Lewis et al. 2012; Hsiao et al. 2014). This is in accordance with the neuropathological studies describing a stereotypical pattern of ventral mesencephalic dopaminergic neurodegeneration resulting in uneven dopaminergic denervation of the STR (Fig. 6b) (Damier et al. 1999; Fearnley and Lees 1991; Waters et al. 1988; Halliday et al. 1996). The decrease in striatal tracer binding significantly correlates with the degree of locomotor disability, particularly with bradykinesia and rigidity (Vingerhoets et al. 1997; Holthoff-Detto et al. 1997; Rinne et al. 2000; Otsuka et al. 1996). Interestingly, it does not correlate with the degree of rest tremor, suggesting that the neural substrate of this motor symptom might be distinct from the nigrostriatal pathway (Otsuka et al. 1996; Vingerhoets et al. 1997). Longitudinal follow-up PET tracer studies have estimated the progression of mesencephalic dopaminergic dysfunction over time and found that presynaptic dopaminergic function declines exponentially, indicating that the progression of the disease tends to be faster at the early phases (Nandhagopal et al. 2009; Hilker et al. 2005). This finding is of potential importance in therapeutic trials

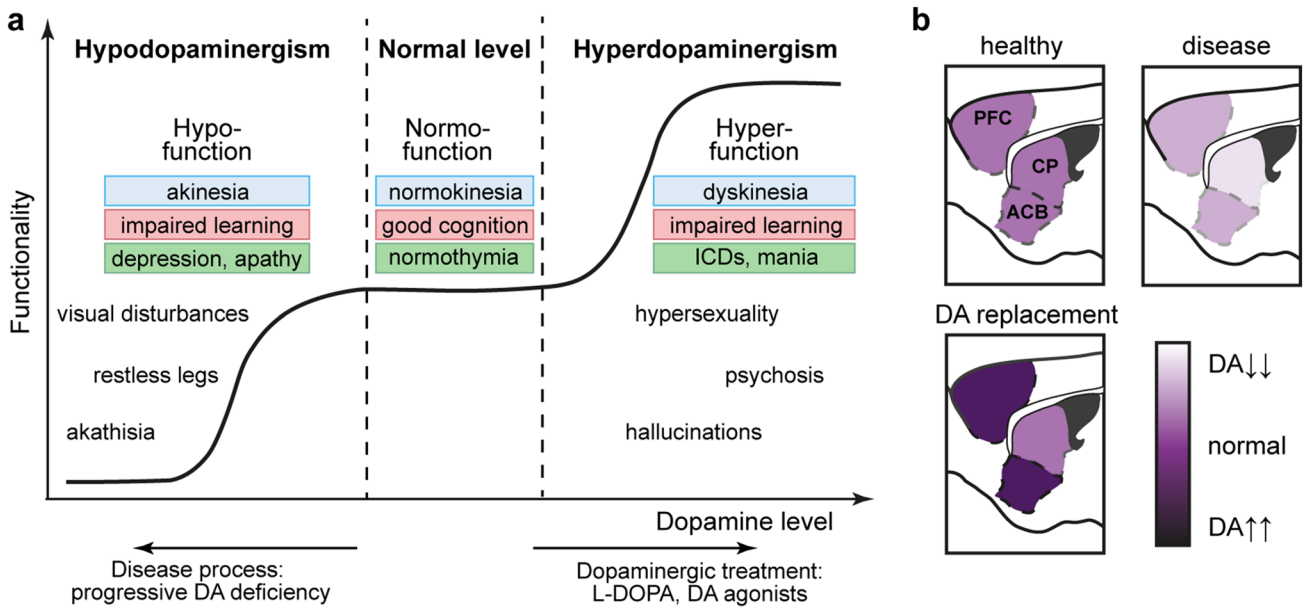

Fig. 6 The relationship between DA levels and physiological functions/dysfunctions. **a** As a consequence of diverse compensatory mechanisms, mild to moderate changes of DA levels remain asymptomatic (plateau). When the severity of hypo- or hyperdopaminergism increases, compensatory mechanisms fail to retain physiological functions leading to dysfunctional neural circuits manifesting as clinical symptoms. Hypodopaminergic states develop as a consequence of disease progression, whereas hyperdopaminergic states emerge as side effects of DA replacement therapy. **b** Ventral mesencephalic dopaminergic (A8–A10) neurodegeneration shows a stereotypical pattern resulting in severe hypodopaminergism in the caudoputamen (CP, nigrostriatal pathway) and mild to moderate hypodopaminergism in the ventral STR (ACB—nucleus accumbens, mesolimbic pathway) and prefrontal cortex (PFC, mesocortical pathway). As a consequence, doses of DA replacement therapy which are necessary to remedy the nigrostriatal pathway simultaneously overdose the mesocortical and mesolimbic pathways

testing compounds with disease-modifying potential, if DAT SPECT is chosen as a surrogate marker for progression of PD. It would mean that such clinical trials should be preferentially performed in de novo PD patients or even in prodromal stages of PD with phenoconversion to manifest motor PD as a clinical end point (see also RBD below).

Distinct behavioral and pharmacological triggers can be used to detect dysfunctional patterns of brain activity and neurotransmitter release. Several studies have been conducted to measure changes of striatal DA release triggered by L-DOPA challenge and correlated this with different symptoms of PD. They have consistently found that L-DOPA induces striatal DA release and that the degree of L-DOPA-induced DA outflow strongly correlated with disease duration (La Fuente-Fernández et al. 2004), Hoehn–Yahr stage (Pavese et al. 2006) and motor disability measured by the Unified Parkinson's Disease Rating Scale (UPDRS) (Tedroff et al. 1996). This means that patients who had a longer disease duration, higher Hoehn–Yahr stages or higher UPDRS scores have larger putaminal DA release upon L-DOPA administration. Furthermore, the amplitude of striatal DA release positively correlated with dyskinesia scores, indicating that a failure in the regulation of DA release contributes to the development of L-DOPA-induced dyskinesias (Pavese et al. 2006, La; Fuente-Fernández et al. 2004), an adverse effect of L-DOPA affecting up to 90% of patients after 10 years of DA replacement therapy (Lopez et al. 2010; Hauser et al. 2007).

Reduction of the hypothalamic ^{18}F-DOPA uptake indicating monoaminergic dysfunction and reduced AADC activity has been reported in PD patients (Pavese et al. 2010, 2011; Moore et al. 2008). However, since the hypothalamus, apart from its intrinsic dopaminergic neurons (A11–A15), receives dense monoaminergic innervation originating from the serotonergic median and dorsal raphe nuclei and noradrenergic A1 and A6 (locus coeruleus) cell groups (Palkovits et al. 1980; van de Kar and Lorens 1979), changes in ^{18}F-DOPA PET reflect the net alterations of all these systems (Pavese et al. 2011). Consequently, direct conclusions on the hypothalamic dopaminergic system (A11–A15) cannot be drawn from ^{18}F-DOPA results. Nevertheless, significant reduction of postsynaptic D_2 and D_3 receptors has been observed in a ^{11}C-raclopride study, indicating dopaminergic dysfunction in the hypothalamus of PD patients (Politis et al. 2008).

Currently, the diagnosis of clinical PD is exclusively based on the presenting symptomatology (Table 1), and neuroimaging techniques such as SPECT, PET or conventional MRI are not recommended as a first-line diagnostic approach. However, under certain conditions (e.g.,

atypical symptomatology or unclear response to dopaminergic treatment), imaging techniques can be of use to better differentiate idiopathic PD from atypical parkinsonian syndromes such as multiple system atrophy (MSA) or progressive supranuclear palsy (PSP) and from secondary causes of parkinsonism (e.g., vascular parkinsonism, neoplasms or drug-induced parkinsonism). DAT SPECT using the ^{123}I-Ioflupane ligand (DATScan) can be used to measure the strength of dopaminergic innervation of the STR (striatal DAT levels) and is thereby able to differentiate neurodegenerative forms of parkinsonism (e.g., PD, MSA, PSP) which normally show reduced striatal DAT levels, from essential tremor and healthy controls (normal striatal DAT levels) (Kägi et al. 2010; Scherfler et al. 2007). However, this technique does not allow further distinguishing idiopathic PD from the atypical parkinsonian syndromes (MSA, PSP). In this case, one could perform a D_2/D_3 receptor SPECT with the ligand ^{123}I-iodobenzamide (^{123}I-IBZM). PD patients generally show normal postsynaptic D_2/D_3 signal intensities, while MSA and PSP patients are commonly characterized by decreased postsynaptic D_2/D_3 receptor availability. However, a normal D_2/D_3 signal does not exclude MSA or PSP (Vlaar et al. 2007). Other techniques to differentiate idiopathic PD from atypical parkinsonian syndromes are metabolic PET imaging with ^{18}F-FDG (Hellwig et al. 2012; Juh et al. 2004), which relies on disease-specific alterations of brain glucose metabolism, or MRI-based approaches such as T2-weighted structural MRI, voxel-based morphometry and diffusion tensor imaging (Price et al. 2004; Paviour et al. 2005; Ota et al. 2013).

At the onset of motor symptoms and, consequently, at the time of diagnosis 30% of nigral cells have already been lost and only 50–60% of normal TH immunoreactivity is present in the STR (Fearnley and Lees 1991; Greffard et al. 2006; Cheng et al. 2010; Kordower et al. 2013). The time period, in which the pathological process of PD has already started but the motor symptoms are not yet present, is the so-called premotor or prodromal phase of PD (Kalia and Lang 2015). During this period, functional neuroimaging of the nigrostriatal system is able to detect subclinical levels of dopaminergic dysfunction and thus facilitate the identification and risk stratification of patients with prodromal PD (Baucknehet et al. 2018; Heller et al. 2017; Meles et al. 2017; Iranzo et al. 2010; Stiasny-Kolster et al. 2005; Piccini et al. 1999). Patients suffering from idiopathic RBD, a parasomnia characterized by the absence of atonia during REM sleep in combination with abnormal nocturnal behavior, represent a specific prodromal risk population for developing PD (Iranzo et al. 2013). Several studies found that RBD manifestation precedes the onset of PD, dementia with Lewy bodies and MSA, thereby representing an early and specific symptom of these neurodegenerative α-synucleinopathies (Postuma et al. 2012; Schenck et al. 2013). Applying DAT SPECT imaging with ^{123}I-Ioflupane on RBD patients revealed a progressive decrease of presynaptic striatal DAT availability from "mild" or "subclinical" RBD to manifest RBD to PD (Heller et al. 2017). Moreover, ^{18}F-FDG-PET imaging showed that a subgroup of RBD patients already possessed the same altered brain glucose metabolism pattern which is related to PD patients (Meles et al. 2017). Taken together, neuroimaging techniques can help to differentiate RBD patients from healthy controls, to monitor RBD disease progression, to stratify the risk of phenoconversion to PD and thereby identify and characterize eligible patients for neuroprotective trials (Heller et al. 2017; Baucknehet et al. 2018).

Symptomatology 'off'/'on' dopaminergic medication: conclusions of clinical studies

Clinical drug studies investigating the potential of dopaminergic medication to improve, but also to worsen or even induce some of the PD symptoms, are valuable tools to identify distinct symptoms which are linked to dysfunctional dopaminergic neurotransmission.

Physiological dopaminergic functions, such as voluntary motor control, require optimal DA levels in dopaminergic output regions. Both a hypodopaminergic and hyperdopaminergic state result in neural network dysfunction and eventually in clinical symptoms. At the time of PD motor symptom onset, around 30% of dopaminergic nigral neurons are lost and 50–60% of their axon terminals show a marked decrease of TH immunoreactivity (Fearnley and Lees 1991; Greffard et al. 2006; Cheng et al. 2010; Kordower et al. 2013). This indicates that even when the disease process had started and moderate DA shortage is present in the STR, intrinsic mechanisms compensate the DA deficit retaining normal physiological functions and thereby an asymptomatic state (Fig. 6a) (Perez et al. 2008; Zigmond et al. 1990; Garris et al. 1997; Bergstrom and Garris 2003; Obeso et al. 2004). Interestingly, patients with incidental LB disease, i.e., healthy individuals without apparent parkinsonism or dementia with LB/LN pathology upon autopsy, show a 27% cell loss of pigmented nigral neurons (Fearnley and Lees 1991) and a 33–50% decrease of striatal TH immunoreactivity (DelleDonne et al. 2008; Dickson et al. 2008; Beach et al. 2008). As PD progresses and the severity of hypodopaminergism increases, the compensatory mechanisms fail and symptoms of a hypoactive dopaminergic system manifest. Replenishment of DA neurotransmission in these hypodopaminergic regions via DA replacement therapy (e.g., L-DOPA, DA agonists) will ameliorate the manifestation of DA shortage (Fig. 6a, b) (Birkmayer and Hornykiewicz 1961; Cotzias et al. 1969). Concurrently, given the uneven nature of neurodegeneration across the dopaminergic systems of the brain in PD, doses of L-DOPA which are

necessary to restore dopaminergic neurotransmission in the most severely depleted nigrostriatal system simultaneously 'overdose' the better preserved mesolimbic and mesocortical brain networks. Thus, dopaminergic treatment with the focus on the primary clinical aim of ameliorating the motor symptoms leads to overactivation of the mesolimbic and mesocortical systems, thereby resulting in symptoms of hyperdopaminergism (Fig. 6b) (Gotham et al. 1988; Swainson et al. 2000; Voon et al. 2017; Vriend et al. 2014; Joutsa et al. 2015; Vaillancourt et al. 2013). Therefore, symptoms of a dysfunctional dopaminergic neurotransmission represent a continuum in which hypodopaminergic states develop as a consequence of disease progression, whereas hyperdopaminergic states emerge as side effects of DA replacement therapy. In the following section, we will briefly give an insight into the dopaminergic symptoms of PD.

The pioneering work of A. Carlsson showed that DA deficiency in the brain of rabbits resulted in parkinsonian symptoms which could be alleviated by administration of L-DOPA, a blood–brain barrier crossing precursor of DA (Carlsson 1959; Carlsson et al. 1957). Since then, both neuropathological and neuroimaging studies of PD patients have shown that the degree of DA deficiency in the dorsal STR significantly correlated with the Hoehn–Yahr stage and UPDRS motor disability, especially with bradykinesia and rigidity scores (Hornykiewicz 1963; Morrish et al. 1995; Broussolle et al. 1999; Seibyl et al. 1995; Hsiao et al. 2014; Pavese et al. 2011; Nandhagopal et al. 2009; Price et al. 1978). Consequently, administration of L-DOPA significantly improves the two latter motor symptoms of PD (Birkmayer and Hornykiewicz 1961; Cotzias et al. 1969). Although dopaminergic replacement therapy is the most effective symptomatic treatment of PD, long-term L-DOPA administration leads to motor side effects, the so-called L-DOPA-induced dyskinesias (LIDs). LIDs are among the most common adverse effects of L-DOPA therapy and affect up to 80% of patients after 5 years and up to 90% after 10 years of treatment (Hauser et al. 2007; Ahlskog and Muenter 2001; Rajput et al. 1984; Jong et al. 1987). The term LIDs refers to a variety of motor side effects which can be classified based on the clinical movement pattern and the temporal correlation between the occurrence of the dyskinesia and the administration of dopaminergic medication (Luquin et al. 1992; Pandey and Srivanitchapoom 2017; Bastide et al. 2015). Interestingly, severe nigrostriatal damage seems to be a prerequisite of LIDs when L-DOPA is administered in pharmacologically relevant doses. Neither healthy controls nor non-human primates with only moderate DA deficiency developed LIDs as a result of long-term L-DOPA treatment (Boyce et al. 1990; Schneider 1989; Hagenah et al. 1999; Di Monte et al. 2000; Jenner 2008). This indicates that nigrostriatal hyperdopaminergism per se is not sufficient to induce dyskinesias, but other factors have to be involved additionally. It is hypothesized that a 'dysregulated DA release' is responsible for the development of LIDs (see above), which originates in the compensatory mechanisms and changes due to dopaminergic denervation of the STR. It was shown that sprouting of serotonergic axon terminals takes place in the STR of PD patients (Rylander et al. 2010). Serotonergic neurons, due to their partially overlapping protein expression with dopaminergic cells (e.g., AADC, VMAT2), are able to take up L-DOPA, convert it to DA and store it in synaptic vesicles (Tison et al. 1991; Arai et al. 1994, 1995; Butcher et al. 1970). As a consequence, these neurons, although do not normally rely on DA as a neurotransmitter, synthesize and release DA upon administration of L-DOPA (Carta et al. 2007). However, since they neither express D_2 autoreceptors mediating the natural feedback of DA release, nor DAT to clear DA from the synaptic cleft, the dopaminergic neurotransmission becomes dysregulated resulting in swings of synaptic DA levels manifesting as LIDs (Mosharov et al. 2015; Carta and Bezard 2011).

Cognitive deficits ranging from mild cognitive impairment (MCI) not yet qualifying as dementia to manifest dementia are common non-motor symptoms in PD with significant impact on the quality of life (Chaudhuri and Schapira 2009). MCI can be observed in prodromal and manifest PD affecting around 20% of patients at the time of diagnosis (Muslimovic et al. 2005; Aarsland et al. 2009a) and displays a major risk factor for the progression to PD dementia (PDD) (Hoogland et al. 2017; Hobson and Meara 2015; Pedersen et al. 2017). Cognitive impairment most commonly affects executive functions, resulting in a 'dysexecutive syndrome' resembling that seen in patients with frontal lobe damage (Owen et al. 1993, 1995; Taylor et al. 1986; Muslimovic et al. 2005; Rowe et al. 2002). The pathophysiology of MCI and dementia in PD is heterogeneous and involves a combination and synergism of distinct pathological changes. These include cortical LB pathology (Mattila et al. 2000; Apaydin et al. 2002; Hurtig et al. 2000; Irwin et al. 2012; Compta et al. 2011), cortical cholinergic deficiency due to the degeneration of the nucleus basalis of Meynert (Mattila et al. 2001; Perry et al. 1991), noradrenergic loss as a consequence of locus coeruleus degeneration, cortical and limbic reduction of DA due to the degeneration of the mesolimbic and mesocortical dopaminergic systems (Rinne et al. 1989; Paulus and Jellinger 1991; Zweig et al. 1993; Ito et al. 2002; Scatton et al. 1983), potential occurrence of Alzheimer's disease co-pathology (Boller et al. 1980; Paulus and Jellinger 1991; Irwin et al. 2012; Compta et al. 2011) and others—for a thorough review see Halliday et al. (2014). This means that a DA deficit in certain brain regions contributes to the cognitive deficit seen in nondemented PD patients with MCI and in PDD patients (Rinne et al. 1989; Paulus and Jellinger 1991; Zweig et al. 1993; Ito et al. 2002; Scatton et al. 1983). However, DA deficiency per se is not considered

to be sufficient for the development of the full range of cognitive deficits (Bosboom et al. 2004; Caballol et al. 2007). Interestingly, studies examining the effects of L-DOPA on PD patients with dysexecutive syndrome report beneficial, neutral and detrimental effects (Gotham et al. 1988; Swainson et al. 2000; Kulisevsky 2000; Downes et al. 1989; Bowen et al. 1975; Kulisevsky et al. 1996; Lange et al. 1992; Pillon et al. 1989). This is because executive functions can be split into different components, such as working memory, inhibition, attentional set shifting and planning, whose neurobiological correlates are distinct (Smith 1999; Rabinovici et al. 2015). During an executive task, depending on the subdomain required, different neural networks are active including the prefrontal and parietal cortices, the basal ganglia, the thalamus and the cerebellum (Collette et al. 2005; Monchi et al. 2001, 2006; Wager et al. 2004; Wager and Smith 2003; Cools et al. 2004). As a consequence, cognitive tasks which rely on DA-depleted brain regions (dorsal STR) will be ameliorated by DA replacement therapy, whereas cognitive functions associated with relatively intact or less affected, DA-dependent brain regions (ventral STR and prefrontal cortex) will be impaired due to a relative 'overactivation' of these systems (Gotham et al. 1988; Cools et al. 2001). This explains why studies investigating the effect of DA replacement therapy on cognitive function report both detrimental and beneficial effects: depending on the cognitive task, distinct subdomains of executive function are examined, all having a different grade of hypodopaminergism.

Neuropsychiatric syndromes ranging from major depression to psychosis and impulse control disorders (ICDs) are highly prevalent in PD affecting the vast majority of PD patients during the course of the disease (Aarsland et al. 2009b). Major depression occurs in approximately 17% of PD patients (Reijnders et al. 2008) and apathy is present in up to 60% (Yamanishi et al. 2013; Pedersen et al. 2009), whereas the prevalence of anxiety in cross-sectional studies ranges between 20 and 49% (Chen et al. 2010; Dissanayaka et al. 2010; Kulisevsky et al. 2008; Nègre-Pagès et al. 2010; Nuti et al. 2004). All three disorders are suggested to be—even if partly—associated with a deficient mesolimbic dopaminergic neurotransmission, i.e., with a mesolimbic hypodopaminergic state (Remy et al. 2005; Voon et al. 2011; Weintraub et al. 2005). This notion is further supported by clinical trials investigating the efficacy of DA agonists in depressive syndromes showing significant improvement of these symptoms (Reichmann et al. 2002, 2003; Barone et al. 2010; Lemke et al. 2005; Pahwa et al. 2007; Bodkin and Amsterdam 2002; Thobois et al. 2013). A wide range of ICDs, such as pathological gambling, compulsive sexual behavior and binge eating, are associated with dopaminergic treatment affecting around 13.6% of PD patients on DA replacement therapy compared to 1.7% of patients receiving neither DA agonists nor L-DOPA (Weintraub et al. 2010). ICDs are suggested to develop as a consequence of a dopaminergic hyperactivity in ventral striatal reward circuitry (mesolimbic system), resulting in an increased drive to perform a certain behavior and to be maintained by an impaired learning from negative consequences due to prefrontal cortical hyperdopaminergism (mesocortical system) (Fig. 6b) (Weintraub 2008; Evans et al. 2006; O'Sullivan et al. 2011; Steeves et al. 2009; Cilia et al. 2008). Interestingly, the largest multicenter study (DOMINION) investigating the occurrence of ICDs in 3090 PD patients found that the frequency of developing an ICD was twofold higher in patients receiving DA agonists compared to patients taking L-DOPA (14.0% vs. 7.2%) (Weintraub et al. 2010). This can be explained by a significantly higher affinity of DA agonists to D_3 receptors compared to D_1 and D_2 receptors (Gerlach et al. 2003). While D_1 and D_2 receptors are more abundant in the dorsal STR (nigrostriatal pathway) mediating voluntary motor control, D_3 receptors are predominantly found in the ventral STR (mesolimbic pathway) playing an important role in reward mechanisms (Sokoloff et al. 1990; Gurevich 1999). As a consequence, doses of DA agonists required to improve motor symptoms may overactivate the mesolimbic system resulting in ICDs (Weintraub 2008; Voon et al. 2017). The association between developing an ICD and a hyperdopaminergic state in the mesocortical and mesolimbic systems is further supported by longitudinal studies showing that DA agonist dose reduction or discontinuation, even in combination with an increased L-DOPA dose, significantly improves ICD symptoms (Mamikonyan et al. 2008).

Concluding remarks

Neuropathological analysis, neuroimaging studies and clinical trials have enabled us to better understand dopaminergic dysfunction in PD. It has become evident that, although being one of the core features of PD, nigrostriatal degeneration cannot be solely accountable for the wide range of PD symptoms. Despite the central role of DA in PD, extramesencephalic, i.e., diencephalic, olfactory bulbar and retinal dopaminergic systems have not been systematically investigated yet—not to speak of the dopaminergic system related to the gastrointestinal tract. The distinct dopaminergic systems have a surprisingly high neurobiological diversity, suggesting that there is not one general type of dopaminergic neuron but rather a spectrum of different dopaminergic phenotypes. This heterogeneity on the cellular level could account for the observed differences in susceptibility of the dopaminergic systems to the disease process. To finally understand which factors render neurons particularly vulnerable, we first ought to investigate which neuronal populations are affected in the course of PD, with emphasis on neuronal cell groups sharing common traits,

such as the synthetic machinery, the metabolism and the overall reliance on DA as a neurotransmitter.

Arvid Carlsson and his fundamental discovery of DA deficiency in PD paved the way for the still ongoing era of dopaminergic replacement therapy and fueled 50 years of research on the dopaminergic systems in PD. Within the last 2 decades, the research focus slowly shifted toward other important areas such as neuropathological research on other neurotransmitter systems involved in PD, identification of genetic mutations or environmental risk factors. A major focus of the basic research field has been set on unravelling the pathogenesis and progression of PD including research on α-synuclein aggregation and interneuronal trafficking on one side and the identification of cell-autonomous factors rendering certain cell groups more vulnerable to the disease process, such as mitochondrial dysfunction or electrophysiological cell properties on the other side.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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