In this review, we approach Parkinson’s disease (PD) in the context of an evolutionary mismatch of central nervous system functions. The neurons at risk have hyperbranched axons, extensive transmitter release sites, display spontaneous spiking, and elevated mitochondrial stress. They function in networks largely unchanged throughout vertebrate evolution, but now connecting to the expanded human cortex. Their breakdown is favoured by longevity. At the cellular level, mitochondrial dysfunction starts at the synapses, then involves axons and cell bodies. At the behavioural level, network dysfunctions provoke the core motor syndrome of parkinsonism including freezing and failed gait automatization, and non-motor deficits including inactive blindsight and autonomic dysregulation. The proposed evolutionary re-interpretation of PD-prone cellular phenotypes and of prototypical clinical symptoms allows a new conceptual framework for future research.

**The Leitmotivs of This Review: From Cellular Biology to Clinical Analysis**

Parkinson’s disease (PD) is the second most frequent neurodegenerative disease in humans. Age is the principal risk factor, with incidence rising exponentially above 60 years [1]. In a previous Personal View paper, we reviewed anatomical and physiological differences between the PD-susceptible structures in the human brain and their counterparts in other mammals [2]. In this review, we first explore the reasons for focal vulnerability of certain cell types. A unifying pattern of high energy demands at multiple levels crystallizes, based on salient studies that will be discussed in detail. We extend the review beyond the commonly accepted focus on dopaminergic cells by showing that there is also involvement of serotonergic, cholinergic, and noradrenergic neurons, all originating in the brainstem or the basal ganglia (BG). With this novel system approach, we link vulnerable networks within an argument related to evolution, based on works of comparative anatomy and clinical neurology. With the input of behavioural evolutionary sciences, we re-interpret key clinical PD syndromes as manifestations of dysfunctional or maladaptive archaic networks. We argue that the structures at risk modulate automated behaviours in response to environmental challenges, and we give salient clinical examples supporting this hypothesis. However, we draw attention to the fact that the available literature does not link this re-interpretation to all PD symptoms, especially when it comes to those appearing lately in the course of the disease. As the arguments develop, we hope to cement the concept that there may be an evolutionary mismatch within the human brain due to the dichotomy between areas (specifically the telencephalon) where cellular numbers and network complexity have increased markedly and areas of the brain that have largely remained static in terms of these indices. These data are closely linked to selective vulnerability of certain cell types and to the evolutionary rooting of PD syndromes.

**Main Mechanisms Impacting PD-Prone Structures**

**Hyperbranchism and Increased Synaptic Density as Economical but High-Risk Connectivity Tools**

In 1997, Parent [3] stated that ‘structures that appear early in the evolution are among the first to undergo involuion in ageing diseases’ and ‘the neurodegenerative processes at play specifically target the most phylogenetically ancient components of the brain, including the SN.’ But how?
Based on immunohistochemical findings, Parent and co-workers suspected that characteristics of the axon are a key to understanding the degenerative process of human PD [4]. Indeed, the human substantia nigra pars compacta (SNc) projections have highly branched terminal regions with an extraordinary number of synaptic release sites. For one dopaminergic neuron reaching out to the human striatum this number has been estimated to be between $1 \times 10^6$ and $2.4 \times 10^6$, with highest values in neurons originating in the lateral part of the SNc [5–7]. In order to maintain the connections, axons develop a high degree of arborization: they become hyperbranched. Although these data suggest primarily an unfavourable ratio of SNc neurons to striatal and suprastriatal cortical neurons, it could also be that the degree of hyperbranchism as well as the number of synapses that one single SNc axon has to form in the human striatum goes up in a secondary, compensatory way when other SNc neurons succumb to the disease process or to old age. Anyhow, it has been estimated that the energy cost of axon potential propagation and synaptic release increases exponentially with hyperbranchism [8] (Figure 1). When taking into account that the length of a single SNc dopamine (DA) neuron exceeds 4 m, it is instantly obvious that the bioenergetic demands associated with such abundant vesicular transmitter release are likely to be daunting [9,10]. Other neurons at risk in PD also have highly branched axons with thousands of transmitter release sites at telencephalic targets, although quantitative estimations as in the case of dopaminergic neuron are currently lacking. For instance, serotonergic neurons from the raphe nuclei have long and highly branched axons that innervate forebrain areas including the striatum [11]. Pedunculopontine cholinergic neurons, locus coeruleus noradrenergic neurons, and lateral hypothalamic orexin neurons, all have long, highly branched axons that innervate the telencephalon (see [12–16] and Figure 2). Of note, the evolutionarily well-conserved melanopsin-containing ganglion cells in the retina also widely innervate various brain structures, including not only their primary target the suprachiasmatic nucleus but also the superior colliculus (SC) and the dorsal lateral geniculate nucleus [17,18]. Beyond this undeniable energy challenge, it has to be questioned how subtle gauging or calibration can be maintained in highly branched systems and how precise feedback should function. Adequate feedback seems to be maintained in early human life, but this is no more the case in PD, as clinically confirmed by less adequate tuning of movements, emotional expressions, and reactions [19]. While efficiently adaptive to development, hyperbranching is at risk for breakdown with age, causing reversion to slower, coarser, and less adaptive behaviours, all characteristic features of PD (see Box 1 on other contributing, deleterious evolutionary mechanisms).

Figure 1. Theoretical Models of Axonal Length and Cerebral Energy Consumption. (A) Mathematical model illustrating the exponential increase of the axonal length with hyperbranchism (from [8], with permission). The authors had estimated that for neurons with 14 levels of branches ($H = 14$), the total axonal length would be about 50 cm, possessing both over 8000 nodes and axonal endings. (B) Estimation of energy consumption of the rat brain (modified, with permission, from [10]). The increased efficiency of action potentials in mammals is taken into account. When extrapolated to Parkinson’s disease-prone neurons in humans with long, unmyelinated, and densely branched axons, the percentage of energy demands of action potentials probably rises again.
Examination of the somatodendritic region of at-risk neurons gives additional insight into the factors that might drive vulnerability. The dopaminergic neurons of the ventral tier of the SNc are slow, autonomous pacemakers with broad action potentials and large oscillations in cytosolic Ca^{2+} concentration [20,21]. While facilitating the pacemaking process, the Ca^{2+} oscillations also drive mitochondrial oxidative phosphorylation and ATP production, by loading juxtaposed mitochondria with Ca^{2+}. This feed-forward bioenergetic control mechanism appears to be phylogenetically old, as it is present in muscle as well [22]. The mechanism ensures that sustained synaptically driven activity in dopaminergic neurons does not fail because of ATP depletion. This is critical in the BG because even short periods of inactivity in dopaminergic neurons would cause suppression in ongoing goal-directed movements, with possibly dire consequences to the organism’s survival. Similarly, noninterrupted activity is crucial for other systems, including those maintaining circadian rhythms, preparedness in the form of arousal changes, and fight and
The feed-forward bioenergetic control system comes at a cost, however, when the induced oxidant stress diminishes the function of mitochondrial Complex I and increases mitochondrial damage and mitophagy. When reaching a critical tipping point, PD-vulnerable neurons (at different sites) go over a bioenergetic ‘cliff’, become senescent, and die. In this context, it has to be mentioned that in the healthy condition the basal rate of oxidative phosphorylation in dopaminergic SNc neurons is already at the near maximal rate sustainable by the mitochondrial network and that the most actively involved mitochondria are located at the most extended arborizations. Notably, the feed-forward design also has a negative impact on axonal trafficking.

Pacemaker Status of PD-Prone Neurons
The feed-forward bioenergetic control allows neurons with extensive cortical innervation to figure as pacemaker cells. Such a tonic level of discharge has been reported for numerous areas at risk for PD involvement, such as the SN, the subthalamic nucleus, the internal and external globus pallidus, the locus coeruleus, the pedunculopontine nucleus, the dorsal vagal nucleus, and the suprachiasmatic nucleus in the hypothalamus. In the gastrointestinal tract the interstitial cells of Cajal and in the retina the melanopsin-containing ganglion cells equally figure as pacemakers, the latter contributing by photo entrainment to the regulation of light–dark rhythm with repercussions on sleep, arousal, mood, etc. Of note, striatal cholinergic interneurons, although being pacemaker cells with highly branched, unmyelinated axons similar to dopaminergic neurons, do not succumb in PD or ageing. The only obvious difference between them and PD-prone neurons is the lack of a long stretch of axon between the terminal field and the cell body. It has also to be mentioned that the mesolimbic dopaminergic pathway

Box 1. PD Deleterious Evolutionary Mechanisms

Evaptation as Utensil for Network Adaptation
Evolution has efficiently progressed by a ‘recycling’ approach with older circuits taking on new jobs. In this perspective the BGs have undergone what is called ‘exaptation’. This is where an ‘ancestral core unit is co-opted for multiple functions’ By changing the input and output targets, these loops simultaneously process different modalities and impact different physiological functions. One set of circuits thus handles emotional, cognitive, and motor functions in parallel, despite increasing complexity of the information input. Can exaptation also increase the vulnerability to the ageing process? Does it lead to higher vulnerability to genetic mutations and environmental toxins? In particular, does human ‘frequent reliance on habitual performance’ strain such systems?

Antagonistic Pleiotropy
Antagonistic pleiotropy has been proposed to explain cognitive decline in old age. The cellular phenotype of PD-prone neurons – pacemaker status, hyperbranching axons – functions well during young age, but succumbs later on. As human SNc dopaminergic neurons have to service larger striatal territories, they are able to transiently – but not permanently – compensate efficiently by producing higher amounts of dopamine than, for instance, mouse neurons. Later on, this same mechanism enhances cellular vulnerability by a human-specific and time-dependent pathological cascade starting with increased mitochondrial oxidant stress and resulting, among others, in lysosomal dysfunction and aSyn accumulation.

Evolutionarily Imposed Trade-offs
Far outreaching, energy-greedy neuronal networks may have been optimal for development during early life, but may become deleterious in late life. This dilemma has been crisply described as ‘a tangle of trade-offs: energy versus function’. In the nervous system the energy demands are enormous: with 2% of body volume the human brain consumes 20% of energy, with synapses requiring the highest portion. Among the energy trade-offs posited to explain telencephalization in humans, the ‘expensive tissue’ hypothesis has been among the most popular, as it proposes an evolutionary trade-off between the size of the human brain and the size of the human digestive tract, which has become considerably smaller than for a primate of human body size. Despite better digestibility of current human food, this places a burden on PD-prone enteric neurons. Other functional trade-offs directly challenge the BG. Among them, bipedal locomotion has to be mentioned. When comparing with quadrupedal walking in chimpanzees, human bipedalism is 75% less costly and attributable to extension of the hip and hindlimb. However, at the BG level, it demands higher organizational complexity when coordinating forward locomotion.

flee responses or active avoidance behaviour. The feed-forward bioenergetic control system comes at a cost, however, when the induced oxidant stress diminishes the function of mitochondrial Complex I and increases mitochondrial damage and mitophagy. When reaching a critical tipping point, PD-vulnerable neurons (at different sites) go over a bioenergetic ‘cliff’, become senescent, and die. In this context, it has to be mentioned that in the healthy condition the basal rate of oxidative phosphorylation in dopaminergic SNc neurons is already at the near maximal rate sustainable by the mitochondrial network and that the most actively involved mitochondria are located at the most extended arborizations. Notably, the feed-forward design also has a negative impact on axonal trafficking.
In the following, we will describe how human evolution may bring in some of the missing pieces. Crucial pieces of the jigsaw puzzle are still missing when modelled in animals or cellular lines, the characteristics of PD-prone neurons discussed earlier do not yet completely reproduce human PD. Observations on Human Evolution with Impact on PD

Observations on Human Evolution with Impact on PD

When modelled in animals or cellular lines, the characteristics of PD-prone neurons discussed earlier do not yet completely reproduce human PD. Crucial pieces of the jigsaw puzzle are still missing (see Boxes 2 and 3). In the following, we will describe how human evolution may bring in some of the missing pieces.

Exponential Telencephalization

We have previously shown that the exponential human telencephalization stresses subcortical nuclei that have not evolved commensurately in size [2]. But why is the human brain approximately three times larger than expected [34] and why do subcortical outreaching neurons in humans have to innervate a much larger number of neurons in the forebrain? Here, changes in gene expression come originating in the ventral tegmental area do not have a comparable, highly branched axonal phenotype and is less affected by PD neurodegeneration [29,33].

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Box 2. Do Animals Living in the Wild Show Clinical PD Signs and Lewy Bodies?

Although clinicians have compared some PD signs with animal behaviour such as reptilian stare or simian gait [162], naturally occurring PD in other species has not been reported, not even in primates [163,164]. However, as PD is usually limited to 2%–3% of aged subjects, could it be that by lack of systemic observations of animals living in their natural environment the small proportion of aged animals affected by PD has been missed? Obviously, most animals in the wild do not reach very old age, as they die of starvation or predation, but rarely of senescence [163]. Yet, one could expect that the impact of senescence should have been observed, at least in a few mammalian species, when one considers that (i) humans keep their pets up to the end of their life; (ii) thousands of wild-type aged mice are housed in research facilities and are closely observed; and (iii) there is scrupulous observation of aged primates living in zoos. Similar to humans, all these mammals develop arthritis, cancer, cardiovascular diseases, but not PD. That said, studies of non-human primates have shown that ageing is accompanied by motor impairments resembling early stage PD [164,166,167].

Moreover, markers of dopaminergic neuron functions decline with advanced age in primates, suggesting that SNC dopaminergic neurons in humans and non-human primates share a vulnerability to ageing [167–169]. Paralleling this decline is an accumulation of ubiquitin-positive inclusions, increased oxidative damage, and neuroinflammation [163,169]. Lewy pathology, which is a hallmark of human PD, is not seen in non-human primates in a natural environment [163,169]. However, in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys upregulation of aSyn has been reported [170], while in mice deletion of aSyn attenuates MPTP toxicity [171].

Possibly, there has not yet been sufficient screening of large numbers of aged animals to rule out the possibility that LB burden might occur. Of note, exclusive LB manifestation in humans is also hard to explain by differences in the aSyn gene or aSyn protein, as aSyn is found in all vertebrates; the cladogram or evolutionary tree of aSyn shows that human aSyn is phylogenetically old, closely related to homologues in chimpanzees, dogs, and cows [172]. Based on the available data, it is still imaginable that with (extreme) ageing LB pathology may appear in non-human primates [163]. Taken together, the presently available studies suggest that primates can clinically manifest at the worst a ‘preparkinsonian’ state with advanced age, however, without typical Lewy pathology as a pathological marker.

Observations on Human Evolution with Impact on PD

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Box 3. Is Experimentally Induced PD in Animals Mirroring Human PD?

Experimental lesions of the dopaminergic neurons innervating the basal ganglia lead to parkinsonian motor symptoms in vertebrates extending from lamprey to primates, arguing that the absence of PD in animals is not a consequence of a fundamental change in basal ganglia function. In particular, rodents after injection of toxins or with SNCA gene overexpression develop a progressive synucleinopathy. In recent years, injection of misfolded synuclein fibrils has been considered the most promising model [70,123,173], although inoculation in the gut or the striatum has to be considered as an artificial disease initiation not reflecting human disease initiation (for review, see [174,175]). Behavioural testing is difficult in mouse models of PD: many non-motor symptoms, eligible as early markers in PD, are poorly characterized in rodents and comprehensive behavioural testing is not feasible or not comparable to humans [176]. To a certain extent, confined questions can be properly answered, for instance: Is there a vagal propagation route? How to recapitulate dyskinesias? However, striking differences between rodents and humans in terms of brain size, complexity of neuronal interactions, and differences in epigenetic or environmental triggers limit the translation of experimental results to the clinics. Of note, although there is intracytoplasmic accumulation of aSyn in mutant animal models, there is no development of mature Lewy bodies. By contrast, in toxin-treated animals, the oxidative stress produces inclusion bodies that resemble early stages of Lewy bodies (for review, see [177]). Thus, rodent models of PD are able to recapitulate distinct PD features seen in humans, but none accurately reflects the complex and slowly progressive pathology that characterizes human PD [178,179].
first into play. During evolution, the expression of the developmental gene NOTCH 2 has changed, and human-specific paralogs have emerged, which cause expansion of cortical progenitors, and therefore of the neocortex [35]. Second, although animals, similar to humans, exhibit considerable ability to learn from experience, the developmental plasticity of the human cortex appears to be more responsive to environmental events [36,37]. Third, in humans there is greater cellular diversity and specialization, which bolsters cognitive, social, and motor capacities and favours increased adaptability and survival in challenging environments [38]. On the downside, these human acquisitions impose higher energy demands on subcortical structures (Figure 1).

Relative Involution of PD-Prone Structures

BG dysfunction is responsible for the core motor symptoms of PD. When the BG become dysfunctional, some neural networks are able to take over the task of directing slowly evolving behaviour toward appropriate goals and away from punishment. Other networks cannot so readily take over the task of generating context-appropriate, rapid, sequential motor habits [6]. While the BG circuitry has not fundamentally changed with evolution, the cortical innervation of the striatum, the largest of the BG nuclei, has substantially grown. The tasks of the striatum are challenging, as it integrates external and internal information [6,39,40], with an enormous convergence of synaptic connections from almost every region of the cerebral cortex onto striatal projection neurons (SPNs) [41]. During human evolution both the striatum and the neocortex have expanded markedly, but the latter to a much larger extent, causing an evolutionary mismatch [2]. For other BG or brainstem areas this mismatch may be even greater, for instance, the amygdala, the locus coeruleus, and the olfactory bulb [2,42,43]. There is probably also relative shrinking of the evolutionarily old enteric nervous system, due to the trade-off between the gut and the brain (see Box 1) [44]. Despite relative regression in size, human subcortical structures widely innervate the cortex and modulate an extensive array of activities [45] (Figures 3 and 4). The dopaminergic axons mediating this control have an extraordinarily large terminal arbour, allowing individual dopaminergic neurons to modulate cortical information processing and storage in a wide array of striatal circuits [46]. Therefore, the burden placed on the striatal circuitry and the dopaminergic neurons innervating it has grown with the evolution of the cortical mantle [47].

Long Lifespan

Human longevity adds the temporal dimension to the burden of PD-prone systems. Beyond the biological prerequisites for life extension in humans [48], anthropology has recently added an interesting societal argument for longer human lifespan in recent human history. As there is longer need for socialization in humans, longer parental care is also needed, which in part is taken over by female caregivers beyond menopause. This hypothesis has been summarized as ‘increased longevity evolves from grandmothering’ [49], and mathematical modelling suggests that grandmothering alone has propelled the doubling of human lifespans in less than 60,000 years [49,50]. Beyond the reproductive age, genetically driven evolutionary adaptations to such a long lifespan appear not to be efficient.

Pathological Hallmarks of PD

Neuronal Death

There are two primary pathological hallmarks of PD: neuronal death and Lewy body (LB) pathology. These two features of PD are not perfectly aligned in space or time [21,29]. The earliest neuronal loss appears in the SNc without discernible LB pathology. Moreover, there is neuronal loss in other brain regions without obvious LBs. However, it has to be emphasized that neuronal death, although most easy to detect by pathological examination, is not the primary event, as will be discussed in more detail later, but rather secondary to synaptopathy which is followed by axonopathy. While it can be argued that the appearance of LB pathology reflects a successful
strategy for sequestering toxic, ‘invisible’ α-synuclein (aSyn) oligomers [51], it is more parsimonious to assume that neuronal loss can happen also in the absence of aSyn or LB pathology. This conclusion is consistent with analysis of brains of familial cases of PD with known genetic mutations where there is no LB pathology [52]. The dissociation is reinforced by studies on subjects which did not manifest parkinsonism but upon autopsy were found to have abundant LB pathology [53].

From Lewy Body to α-Synuclein

The debate on the role of LB pathology – whether pathogenetic, protective, or just an epiphenomenon – has nurtured numerous discussions, but is beyond the topic of this review (for review, see [54,55]). Despite the earlier appearance of neuronal loss, LB pathology is in most cases an authoritative biomarker, indicating the brain areas where the disease process has been or is still active (Figure 4). In the brain, aSyn is one of the most abundant cytoplasmic proteins, comprising approximately 1% of the cytosolic protein content [56]. It is a major constituent of LBs, and different types of aSyn deposits (dots, Lewy neurites, and LBs) have been identified in various neuronal groups and neuropil [57]. The complex role of aSyn for initiation of the disease at the synaptic level will now be reviewed.
From Synaptopathy to Axonopathy

Synaptopathy is the earliest step in the PD cascade. It is expressed by reduced synaptic plasticity and decrease in transmitter release. It leads to axonopathy, and finally, cellular death. Although αSyn is expressed throughout the brain, dopaminergic neurons are the most vulnerable to its over-expression, as αSyn directly regulates DA levels [58–60]. In axon terminals normally functioning αSyn is tightly bound to membrane on synaptic vesicles [51]. It forms αSyn oligomers or protofibrils, which have the potential to pierce the lipid membrane. Post-translational modification such as phosphorylation or subsequent aggregation further modifies the distribution of pathological deposits. The accumulation of oligomers and protofibrils affects neurotransmitter release by several mechanisms. There is an impairment of the synaptic vesicle pools, change in the distribution and concentration of proteins at the presynaptic complex, and consecutive impairment of docking and fusion of synaptic vesicles at the active zone. The process of misfolding and aggregation of αSyn spreads through the axons to the neuronal cytoplasm [60], where aggregated protofibrils are sequestered in LBs [61]. The elevated cytosolic Ca^{2+} and reactive oxygen species found in vulnerable neurons favour αSyn misfolding and aggregation [62]. A centripetal gradient of αSyn deposits can be visualized: suppressed visibility of normal αSyn in axon terminals, but enhanced visibility of aggregated αSyn in proximal axons and soma [61]. The aggregation of αSyn interacts with mitochondrial dysfunction [63], eventually creating a potential death spiral.
Thus, the predominant role of aSyn pathology with only secondarily occurring cell death is most evident, whereas neuronal count, which represents only the local density of neurons, provides little insight into pathological interactions between aSyn and mitochondria [64]. Reversed sequence of pathology is also possible, with, first, misfolded aSyn disrupting axonal transport and then contributing to axonal pathology [14,65]. In all these scenarios, the demands of telencephalization crucially favour the initiation of the pathogenetic cascade.

From Local Seeds to Propagation Routes
DA toxicity also leads to aSyn deposition [66]. But neither DA nor aSyn alone can explain the following propagation process. Based on animal work and theoretical modelling, it has been shown that anatomical connectivity and local variability of aSyn expression are the main propagation drivers [67]. DA-independent processes of degeneration are also at work as shown by LB-prone neuronal groups beyond the SNc. These areas utilize other neurotransmitters, but are similarly characterized by hyperbranchism of thinly myelinated or non-myelinated axons. Therefore, they constitute independent and separate local seeds for initiating the degenerative process [14,33,67].

Prionlike propagation of misfolded aSyn fragments is presently vigorously debated [14,54,68,69]. While robustly replicated in animal models [70], such propagation is challenging to reconcile with the patterned distribution of LB pathology in the brain of PD patients, our present knowledge on brain connectomics, and the rapidly devastating spread of prototypical human prionopathies [21,54]. However, while this mismatch does not at all exclude such prionlike propagation of aSyn pathology, regional or cell-autonomous mechanisms, as proposed here, must also be factored into pathogenesis [33,71].

Revisiting the Clinical Symptoms of PD from an Evolutionary View

Deficient Automated Body-Environment Reactions and Escape Behaviours
Lack of Automated Leg and Arm Movements
The control system for locomotion shares similarities in its design across all vertebrates, including humans [72]. Crucial networks regulating gait automatization are located in the BG, mesopontine region, and in lower parts of the spinal cord. Here, the central pattern generators are responsible for selection, sequencing, and timing of both the gait and the standing position [73-75]. For a mammal, the time it takes from conception until it starts walking is linearly correlated with brain weight, with humans and elephants at one extreme of the spectrum and mice at the other [76]. In other words, the larger the brain, the longer it takes to reach coordination between the forebrain and lower systems related to locomotion and posture.

PD patients lose internally cued and automatic gait patterning. When they walk, they are plagued by festination, as well as halting at the beginning of ambulation. The loss of natural patterns of locomotion is characterized by compromised stride, stance, and pivoting. Gait impairment in PD has traditionally been considered to arise from deficient BG control of the mesopontine locomotor command centres, including neurons in the pedunculopontine nucleus [73,77]. While not yet examined in detail, it is possible that the PD process directly involves dysfunction of the central pattern generator neurons in the medulla [78]. To compensate for dysfunctional gait automatization, PD patients must consciously focus their attention on ambulation (not talking while walking). They use external visual or auditory cues to overcome festination. Arm swinging, reminiscent of quadrupedal gait pattern, is missing in PD patients [79], who benefit from Nordic Walking which somehow restores quadrupedal forward motion [80]. In other words, PD patients learn to bypass the BG control of the locomotor system and adaptively rely directly on visuomotor control via the corticospinal system. In advanced disease, PD patients have to use this ‘alternative’ pathway on a continual basis. Physiotherapy of PD patients uses strategies to activate attentive
cortical control of walking, including attention to larger stride and full arm swing. However, there is poor long-term outcome in terms of learning or transferring into new automatic behaviours, suggesting that the ‘software’ of the automatic gait pattern can no longer be ‘reprogrammed’, because these pathways are irreversibly disrupted.

**Freezing Instead of Active Avoidance or Escape**

When confronted with dangerous situations, humans can choose among three reactions: torpor or freezing; flight or escape; and active avoidance as the most elaborate behaviour. Often, people identify warning signals and just avoid potentially dangerous situations. PD patients, however, hesitate or ‘freeze’ when encountering an obstacle during walking. Figuratively, they also ‘freeze’ in terms of diminished body expression, halting language, and delayed decision making [81]. This hesitancy is a maladaptive response, often associated with anxiety, sometimes to the point of inexplicable panic and high frustration. For long-term survival, escape, and even better, active avoidance tend to be much more effective than freezing.

How do these two patterns of behaviour – escape and active avoidance – become dysfunctional in PD? While there is no definitive explanation, the neural pathways underlying these behaviours are known, and may offer important clues. It is known for instance that pathways involved in active avoidance include the pedunculopontine nucleus, the SC, and the habenulo-raphe circuits [13,23,82]. Disinhibition of neurons in deeper SC layers is required for responding adequately to a visually perceived stimulus [83]. These tectal-evoked motor responses are modulated by direct dopaminergic input from the SNc [23,84,85]. Furthermore, to trigger active avoidance, the pedunculopontine nucleus is also under the control by the pars reticulata of the SN [83]. Finally, rapid switching of the attentional focus, required to proactively change motor or cognitive directions, is influenced by the noradrenergic pathways originating in the locus coeruleus [86]. In PD, atrophy or local LB deposition has been reported for all the involved areas [87,88].

To escape, immediate heart rhythm acceleration is needed. Therefore, when locomotion is initiated, the mesopontine locomotor command centres also trigger the necessary increases in respiratory and cardiac activity [77]. Since there is deficient BG control of the locomotor command centres in PD, the related cardiac control also becomes dysfunctional. While asymptomatic individuals with reduced heart activation (chronotropic insufficiency) in standardized cardiac stress tests are at higher risk for later development of PD [89], reduced noradrenaline-driven heart activation in PD has been suggested by reduced uptake of meta-iodobenzyl guanidine, a noradrenalin analogue, at the presynaptic terminal of postganglionic axons of cardiac sympathetic nerves [90]. Loss of these axons is not only found in PD patients, but also in patients with rapid eye movement (REM) sleep behaviour disorder (RBD), considered to be a forerunner syndrome of PD (discussed later). Finally, in a study conducted in PD patients living in a war zone, under the threat of missile attacks, the subjects only rarely showed paradoxical kinesia triggered by a visual threat cue, like the flight of somebody else, but, by contrast, frequently reported the experience of gait freezing [91].

**Blindsight**

For precision walking and immediate reaction to visual stimuli, visuomotor coordination is important. Substantial visual information is provided to the SC, the mammalian correspondent of the reptilian tectum opticum [92]. Does the information communicated via this pathway necessarily reach conscious perception, or can it bypass the visual cortex and remain subconscious? The latter is the case, at least in some situations, as demonstrated by ‘blindsight’ – an evolutionarily archaic and subconscious visual perceptive behaviour that efficiently and rapidly handles vitally crucial visual information. It shapes our protective fear system [93]. With functional blindsight,
subjects unconsciously detect motion and correctly ‘guess’ the location of a stimulus. Grasping saccades are initiated before subjects consciously detect the object having triggered them. The responsible phylogenetically old and subconscious pathways are partially overlapping with equally old emotion pathways [94]. SC neurons are tonically inhibited at rest by the BG, but disinhibited in action [94]. For doing so, the same SNc neuron sends one axonal branch to the striatum and another one to the SC [84].

In PD, increased activity of the SN pars reticulata consistently maintains pathological inhibition of the SC [95]. In patients with LB dementia, neuronal loss and aSyn within LB occur in the deep SC layers [96]. Other areas involved in blindsight such as pulvinar, claustrum, and the amygdaloid subnuclei of the amygdala also show molecular changes, neuronal cell loss, and more rarely LB burden in PD patients [97]. Dysfunction of these pathways induces a disruption in blindsight so that PD patients become ‘blind to blindsight’: although they fully conserve conscious vision and can perform movements induced by conscious vision, they can no more rely on crucial, immediately transmitted subconscious visual information about their environment. Therefore, they become unable to instantly react to such stimuli [97]. Missing components of blindsight in PD patients include reduced motion perception and deficient grasping saccades. PD patients show only blunted eye blink startle reactions, and their sympathetic skin conductance is reduced when viewing photos showing fear, disgust, or violence [97,98].

To summarize these deficits, PD patients lose access to evolutionarily old, automatized behavioural patterns underlying our interactions with the external world. They have to apply alternative and conscious ‘mind-directed’ behaviours, which may be slow, strenuous, or even inappropriate from the adaptive-behaviour point of view (Figure 3).

**Loss of Precise Neuromodulatory Tuning**

**Olfactory Dysfunction**

One of the earliest possible manifestations of PD is the loss of olfaction [99]. The olfactory bulb has its own set of DA neurons, an evolutionary-conserved neural population existing from lamprey to mammals [100,101]. Progenitor cells are provided to the olfactory bulb by the equally phylogenetically old rostral migratory system [102]. In humans, there is involution of the olfactory system, and the epithelial surface is much smaller than, for instance, in dogs (2–4 cm² in contrast to 18 cm²) [103].

In PD patients the number of olfactory bulb DA neurons is – paradoxically enough – increased, perhaps related to the aforementioned migratory stream system [104]. The olfactory bulb is heavily loaded with LB [105]. Up to 90% of PD patients show substantial olfactory impairment in terms of poor odour identification, discrimination, and detection thresholds [106]. Missing olfactory input leads to dysfunctional pondering (modulation) of various sensory experiences. For instance, PD patients have impaired perception of disgust communicated via facial expressions [107]. More generally, connections between the olfactory tubercle and the ventral striatum provide olfactory background information that may also influence the dopaminergic reward system [108].

**Defective Light Entrainment**

Light entrainment of the circadian clock is mediated by the evolutionarily old mechanism of phototransduction induced by melanopsin-containing retinal ganglion cells (mRGCs). In humans, mRGCs represent only about 1% of the retinal cell population [109]. This subconscious system mediates non-image-forming responses to photoentrainment, and it communicates with the endogenous biological clock in the suprachiasmatic nucleus. Clock regulation by light–dark rhythm has repercussions for numerous circadian-modulated physiological processes such as...
sleep, arousal, mood, motor activity, and food intake [31]. In PD, the number of mRGCs, which as mentioned is relatively small in humans to start with, is further reduced, and the plexus formed by these cells shrinks [110,111]. At autopsy, aSyn immunoreactivity in the retina and LB burden of the suprachiasmatic nucleus are seen [112,113]. Perturbations of circadian rhythms are frequent in PD patients, who often show excessive daytime sleepiness, and, at more advanced stages, complete inversion of the sleep–wake cycle. Sleep–wake dysregulation has been related to mood, nutrition as well as subtle memory problems in PD patients [114].

Unbalanced Autonomic Reactions

Striking similarity in the arrangement of the autonomic system exists among different vertebrates [115,116] and the development of the mammalian sympathetic and enteric neurons shows astonishing similarities with the development of comparable structures in avian species and zebrafish, with conservation in part of the same transcriptional regulators. The enteric nervous system has even been ranked as the ‘first brain’, because it develops earlier and independently from the central nervous system. There is intense bidirectional dialogue between these two systems, mediated by the vagal nerve and its branches [117,118]. In PD, cutaneous autonomic innervation is decreased. There is greater aSyn burden in peripheral autonomic nerves in PD patients than in controls [119]. The amygdala, as a central autonomic regulator, shows LB burden in its evolutionary-oldest medial parts [120], and functional neuroimaging provides evidence of amygdalar network dysfunction [121]. Disease initiation at the subepithelial level of the enteric nervous system, and – possibly bidirectional – propagation via the vagal are presently debated [122–124]. LB burden at the gut level is often discussed in this context, although it cannot yet serve as a diagnostic marker for PD [125]. Chronic constipation in middle age, reported to be a risk factor for PD [126], could be due to deficient modulation of bowel movements by the interstitial cells of Cajal. These cells share the PD characteristic cellular phenotype [127]. There are other unbalanced autonomic reactions in PD, including paradoxical nocturnal blood pressure rise, orthostatic hypotension, insufficient thermoregulation, and hypersalivation.

Disclosure of Archaic Behaviours and Motion Patterns: REM Sleep Behaviour Disorder

RBD is a PD forerunner syndrome, frequently preceding the core motor syndrome by years to decades. It can also develop in concert with the core motor syndrome of PD [128]. The underlying responsible brain areas regulating RBD include the subcoeruleus/coeruleus complex [129], an area with relative involution in humans [130]. RBD is characterized by episodic loss of physiologic muscle atonia during REM sleep as well as by ‘acting out’ of dreams, most often with a vivid, even violent content [128,131]. The PD process affects the locus coeruleus, among others, and RBD symptoms reflect the degeneration of these subcortical systems. Remarkably, PD patients show a striking restoration of natural movement speed and vigour during an RBD episode [132]. The explanation could be that underactive BG outflows are circumvented by a direct cortical activation of brainstem areas in charge of movements, as shown by single-photon emission computed tomography (SPECT) neuroimaging [133]. The evolutionary significance of RBD remains unexplained. During phylogenetic evolution and our own ontogenetic evolution, body movements during sleep (active sleep) are a natural phenomenon. Therefore, it has been hypothesized that very early dysregulation of neuromotor systems in sleep could, later on, cause RBD [134]. REM sleep is also considered as a ‘protoconscious state, providing a virtual reality model of the world that is of functional use’ and that it ‘prepares for instinctual responsiveness’ [135]. Having the astonishing restoration of movements during RBD in mind, De Cock and colleagues [132] proposed therefore that these ‘archaic movements, determined by central pattern generators in the mesencephalon, pons and spinal cord, serve innate motor behaviours essential for survival’.
Re-interpretation of these various clinical findings suggests that there is loose neuromodulatory tuning of various sensory or autonomic systems, and, less frequently, re-emergence of now useless, archaic reaction patterns.

**Limitations and Open Debates**

**One Theory Cannot Answer All Aspects of a Puzzle**

Our proposal is derived from clinical PD studies and basic research in comparative evolutionary biology, microscopic neuropathology, and cellular neurophysiology. Evidently, there are knowledge gaps in-between and the proposed bridging may occasionally be daring. It is still not known, for instance, whether the characteristics of the proposed cellular phenotype (i.e., hyperbranched axons, extensive transmitter release sites, and elevated mitochondrial stress) are always linked together. It is also not known whether neurons that partially or completely lack this cellular phenotype consistently escape the PD degeneration process. It is possible that there are other, yet to be discovered, evolutionary mechanisms triggering vulnerability to the PD process. Open questions remain, such as to what extent the pedunculopontine nucleus displays spontaneous spiking despite its wide cholinergic and non-cholinergic connections [13,20]? Or, why is the cerebellum largely spared by the disease process? Could it be because the cerebellar efferent pathways are not hyperbranching open systems and function by other feedback mechanisms? Finally, what about early, although mild dysexecutive symptoms [136]? Are they sufficiently explicable by disrupted activation of the forebrain by brainstem originating pathways, for instance, those originating in the locus coeruleus [137]?

**Human Ageing: A Sufficient, Alternative Explanation?**

Can the ageing cascades alone explain the occurrence of PD? At the biological level ageing is not only ‘the result of a build-up of stochastic damage but rather a product of regulated processes’ [138]. Somatic mitochondrial DNA mutations induced by oxidative damage also accumulate with age and DA loss occurs naturally while getting older. Nevertheless, ageing alone cannot explain the distinctive pattern, the magnitude, and the trajectories of pathology seen in PD. Rather than being the consequence of one factor, the pattern of PD pathology likely reflects the convergence of at least three factors: ageing, the cellular phenotype, and telencephalization. This tripartite coalescence creates a distinctive and identifiable combination of bioenergetic, oxidant, and proteostatic stress that leads to mitochondrial dysfunction and accumulation of intracellular protein aggregates. Hence, it is reasonable to hypothesize that with ageing and constant use of the PD-prone systems, a ‘tipping point’ is reached in vulnerable neurons that results in their dysfunction. In this perspective, the long lasting ‘reliance on habitual (motor) performance’ in humans may be a crucial risk factor for nigrostriatal and brainstem originating degeneration [7].

**Other Open Debates**

First, what is the role of lifestyle and environmental factors? Exposure to pesticides, previous traumatic injury, reduced physical activity, intake of dairy products, etc. have been brought into play [139,140]. By intervening in the pathogenetic cascades by yet unknown mechanisms, they may contribute to the interindividual variability of the disease. Second, what is the pathological signature of secondarily manifesting symptoms? While early clinical symptoms are due to involvement of the described cellular phenotype, this may no more be the case for those appearing later in the disease course. For instance, the loss of dopaminergic signalling by the BG results later in striatal atrophy [141]. Although late LB deposition in the cortex is a characteristic finding in advanced PD, it is usually modest in comparison to the brainstem and subcortex. Secondary involvement may follow prionlike propagation routes, but also Wallerian degeneration or be due to other secondary processes [14,21,57,68].
**Future Perspectives**

From Hierarchical Concepts to Evolution-Driven Connectomics

Modern concepts of connectivity (connectome) emphasize the ’boundless’ way of cerebral functioning with, however, specific hubs of the connectome acting as disease-specific critical network epicentres [142]. Strikingly, most nuclei and networks affected in PD are such highly connected ’hubs’ or critical epicentres, despite retaining evolutionarily old network structures. In PD hub dysfunction with changes in nodal organization ranging from erroneous or initially compensatory hyperactivity – for instance, of the default mode network – to complete disconnection have seen reported (for review, see [143]). Recession of the default mode network and disruption of coherence between nodes of a system have been linked to disease initiation. These changes lead to higher oxidative stress favouring the neurodegenerative process (for review, see [144]). Functional neuroimaging such as maps of glucose metabolism outperform structural maps of neurodegeneration in PD [145]. Of note, disease repercussions may also be mediated by dysfunctional oscillations, such as thalamocortical dysrhythmia [146], recently applied to hallucinations and functional syndromes in PD [147].

Proposals for Future Research Avenues

Research in different domains could help test the hypotheses discussed earlier, and corroborate prior findings. First, in human studies, we propose to focus on the pathophysiology of different neuronal cell groups with the aforesaid cellular phenotype, the specific challenges of energy supply in distant axons, and the long-life stress of mitochondria, in particular in the very distant axonal parts of neurons. As there are commonalities between the long-stretched BG neurons and neurons in sympathetic ganglia or the enteric nervous system, these long-stretched and more easily accessible neurons should be studied in more detail in PD [148]. Second, future research could analyse if there are regionally specific vulnerability factors such as the proteins synthesizing the transmitters and modulating their release [149]. Third, the long-term follow-up of well-characterized cohorts such as the Parkinson’s Progression Markers Initiative could bring in further insight [150]. Fourth, it will be important to systematically observe motor and behavioural changes of aged non-human primates or other mammals living in the wild. Ideally, brain autopsies in these animals should confirm the presence or absence of LBs. Further research proposals are outlined in Outstanding Questions.

Concluding Remarks

Our review has focused on the evolution-driven characteristics of the cellular phenotype prone to PD. Through these discussions, we make the case that clinical PD symptoms are a direct consequence of the dysfunctional networks responsible for automatic and reflexive behaviours. However, the proposed model is not without limitations, as discussed in the previous section. Nevertheless, we are hopeful that it will kindle research interest in the evolutionary contributions to PD, which we would argue is a fundamental aspect to consider for comprehensive understanding of the disease’s pathophysiology. This perspective also aligns with developments in the context of other brain diseases, in which human evolution has been recently highlighted [151–153]. Despite current knowledge gaps, we argue that the evolution-driven changes of brain anatomy and function, together with the bioenergetically demanding cellular characteristics, are cornerstones of PD vulnerability in humans, further boosted by the long human lifespan. The disease starts at the synaptic level of long axons and it follows a centripetal progression. Prionlike propagation may invade secondarily other neurons of the same network. Some pathways may be especially susceptible or ‘easy to travel’ such as those starting in the olfactory bulb or those starting in the enteric nervous system and travelling back to the dorsal motor nucleus of the vagal nerve [154]. Disease seeding can develop more or less synchronously in different areas of the central nervous and autonomic peripheral nervous systems and the concept of an

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**Outstanding Questions**

In evolutionarily old structures, are axonal hyperbranching, high numbers of synapses, and feed-forward control of mitochondrial respiration frequently or even always linked? If not, which PD-prone structures show an exception and how are they organized?

Conversely, are evolutionarily old nuclei without this physiological phenotype resistant to PD pathology?

What are the subcellular mechanisms at the synaptic level that launch the degenerative process?

How are aSyn deposition, energetic failure at the mitochondrial level, and axonal degeneration linked together?

To what extent are these pathoanatomical and pathophysiological changes different in humans in comparison with non-human primates and other animals? Are these fundamental differences between humans and other species, or is the difference mostly a matter of lifespan, that is, the existence of irreversible tipping points that are simply not reached during a normal animal life?

Beyond the nigrostriatal system, which other systems are most vulnerable to excessive energy demands placed by the highly developed human neocortex? Is there a qualitative or rather quantitative difference between the human and primate brain?

Why is there interindividual variability in clinical expression and trajectories? Can this variability be tracked back to the cellular level?

Are there epigenetic factors acting locally or yet to be discovered genetic vulnerability or protection factors?

Will therapeutic strategies be found to halt the process of failing cellular energy supply? Are there irreversible tipping points in the neurodegenerative process, with treatment being ineffective beyond them? Are such tipping points due to critical reduction of cellular connectivity?

Will we be able to better distinguish evolution-driven clinical syndromes from secondary compensatory syndromes?
‘in-series’ and stereotyped, sequential, presumably linear, pattern of disease progression can be questioned. Local factors are responsible for local spreading intensity and speed. Parallel, rather than the sequential development of pathology in different systems from the beginning is also compatible with neuroimaging findings: In RBD patients, there is denervation in the forebrain of noradrenergic pathways originating in the locus coeruleus [137]; PD patients suffering from fatigue have concomitant striatal and limbic serotonergic dysfunction [155]. Taken together, these data argue that PD pathology is not staged in a predictable, sequential manner, but rather is variable and capable of arising in several regions at the same time.

Constraints irreversibly imposed by evolution are evident. As clinical PD usually develops only after reproductive age, there is no evolutionary pressure to select against the disease or to select the best cortical–subcortical ‘matches’. As such, even with better understanding in neurochemistry and cellular structure, we view the human nigrostriatal and other archaic pathways as implicitly vulnerable with a continuing risk for degeneration with progressive age.

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Disclaimer Statement
The authors have no conflict of interest to declare.

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