Review

Understanding cognitive deficits in Parkinson's disease: lessons from preclinical animal models

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Parkinson's disease (PD) has been, until recently, mainly defined by the presence of characteristic motor symptoms, such as rigidity, tremor, bradykinesia/akinesia, and postural instability. Accordingly, pharmacological and surgical treatments have so far addressed these motor disturbances, leaving nonmotor, cognitive deficits an unmet clinical condition. At the preclinical level, the large majority of studies aiming at defining mechanisms and testing novel therapies have similarly focused on the motor aspects of PD. Unfortunately, deterioration of the executive functions, such as attention, recognition, working memory, and problem solving, often appear in an early, premotor phase of the disease and progressively increase in intensity, negatively affecting the quality of life of ~50%–60% of PD patients. At present, the cellular mechanisms underlying cognitive impairments in PD patients are largely unknown and an adequate treatment is still missing. The preclinical research has recently developed new animal models that may open new perspectives for a more integrated approach to the treatment of both motor and cognitive symptoms of the disease. This review will provide an overview on the cognitive symptoms occurring in early PD patients and then focus on the rodent and nonhuman primate models so far available for the study of discriminative and spatial memory attention and learning abilities related to this pathological condition.

Cognitive deficits in Parkinson's disease

Parkinson's disease (PD) is a chronic neurodegenerative disorder affecting over four million people worldwide (Dorsey et al. 2007). It is classically characterized by the emergence of motor symptoms such as rigidity, tremor, postural imbalance, and bradykinesia/akinesia (Braak et al. 2003; Jankovic 2008). However, PD also involves nonmotor symptoms (NMS) (Chaudhuri et al. 2006; Jankovic 2008) that appear in the early, often premotor, phase of the disease (Abbott et al. 2005; Abbott 2007; Claassen et al. 2010) and significantly contribute to the impairment of the quality of life of ~50%–60% of PD patients (Aarsland et al. 2012).

Among others, NMS include olfactory dysfunction, REM sleep disorder, neuropsychiatric disturbances, and cognitive deficits (Schrage et al. 2004; Chaudhuri and Odin 2010). All these symptoms develop independently from each other in the early phase of the disease, and progressively increase in intensity, often leading to dementia in the late phase (Cools et al. 2001; Goetz et al. 2008).

Neuropsychiatric mood-related disorders are rather common in PD (Cummings 1992; Schrage et al. 2004) with a prevalence of ~20% (Reijnders et al. 2008), and manifest as apathy, depression, and anxiety.

On the other hand, cognitive impairments associated with PD are mainly related to the executive functions, resulting in a phenotype resembling that of frontal lobe patients (Robbins and Arnsten 2009), with deficits in attention (Ballard et al. 2002), planning, concept formation, and working memory (Kehagia et al. 2010). In particular, memory deterioration affects both spatial (Levin 1990) and nonspatial working memory domains (Matison et al. 1982), implicit memory (Heindel et al. 1989; van Asselen et al. 2009), episodic memory, and procedural learning (Dujardin et al. 2003), whereas the ability to form new episodic memories is preserved (Knowlton et al. 1996; Squire and Zola 1996; Dubois and Pillon 1997). Deficits in visual perception

(Levin 1990; Lee et al. 1998) and object recognition (Laatu et al. 2004) are also frequently reported as one of the earliest symptoms in PD patients, with an apparent independency from the severity of motor dysfunctions, neuropsychiatric complications, and general cognitive deterioration (Girotti et al. 1988; Antal et al. 1998).

The heterogeneity of the cognitive deficits in these patients significantly complicates the clinical diagnosis that is nowadays based on neuropsychological tasks for language (Boston Naming Test), planning and abstract reasoning (Wisconsin Card Sorting test, Tower of London, Wechsler Adult Intelligence Scale [WAIS] similarities), visuospatial abilities (Line Orientation test), free-recall verbal (Rey Auditory Verbal Learning test) and visual memory (Faces Immediate Recognition test), psychomotor speed (Digit Symbol Test), and attention (Digit span backward). However, among them, the memory tasks are the most suitable for PD diagnosis (Muslimovic et al. 2005). Based on that, and despite the lack of uniform diagnostic criteria for PD cognitive impairment (Goldman and Litvan 2011), the diagnosis is usually reached after demonstrating impairments in at least one domain among memory, visuospatial, and attention/executive impairment (Litvan et al. 2011).

As a potential important contribution to the diagnosis of PD cognitive deterioration, there is an increasing effort in the identification of biomarkers such as cerebrospinal fluid, and genetic and neuroimaging biomarkers. However, at present, both an unequivocal clinical definition and a clear pathophysiological knowledge of the cognitive symptoms in PD are still matters of debate.

In fact, whereas the motor impairment is considered to be mainly caused by the progressive degeneration of the dopaminergic nigrostriatal pathway, the etiopathology of the cognitive decline associated with PD is still unknown (Dubois and Pillon 1997; Chaudhuri and Schapira 2009). Clinical studies based on functional imaging techniques (Carbon and Marie 2003) suggest that cognitive symptoms might not only be partially dependent on the death of dopaminergic neurons in the substantia nigra, but also linked to the consecutive involvement of other brain regions, such as prefrontal cortex (Owen 2004), hippocampus

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(Bruck et al. 2004), and amygdala (Ray and Strafella 2012). These data are also supported by preclinical results showing that, in experimental parkinsonian models, the animals are impaired in behavioral tasks mainly mediated by brain areas other than the striatum, such as the hippocampus or the prefrontal cortex, as reported above. Notably, it seems that cognitive deficits in PD patients emerge from tests sensitive to frontal lobe dysfunction (i.e., attentional set-shifting task) and then progressively, as the disease develops, affect tests involving more posterior cortical regions (i.e., visuospatial learning and memory performances) (Owen et al. 1992, 1993, 1997).

Moreover, increasing evidence suggests that the cognitive decline reported in PD patients is not simply related to a mere dopaminergic deficit. Indeed neurodegeneration in PD, besides affecting dopaminergic neurons in the substantia nigra, also appears in the locus coeruleus, the main noradrenergic site (Vazey and Aston-Jones 2012), the raphe nuclei, location of serotonergic neurons (Fox et al. 2009), and the nucleus basalis of Meynert, part of the basal forebrain cholinergic complex (Bohnen and Albin 2011). Thus, the fine balance among the dopamine, noradrenaline, serotonin, and acetylcholine brain systems is massively disrupted.

In line with a heterogeneous neurobiological substrate of the disease, whereas motor symptoms are successfully treated with dopamine replacement therapies, such as L-DOPA administration, cognitive symptoms are only partially responding to these drugs (Kulisevsky et al. 2000). Noteworthy, it has long been debated whether dopamine replacement medications, while improving motor symptoms, have a deleterious (Antonini and Cilia 2009), beneficial (Lange et al. 1992; Pessiglione et al. 2005; Costa et al. 2009), or no effect (Sahakian et al. 1988) on the cognitive impairment in early PD patients. In this regard, it has been suggested that the positive or negative effects on cognitive ability could depend on the severity of the disease and the specific skill being tested.

However, not only are there no available drugs able to revert both motor and nonmotor PD deficits, but also there is no specific suitable treatment for NMS with therapies commonly used in non-PD patients, without taking into consideration the coadministration of typical antiparkinsonian drugs to these patients. Thus, in order to identify specific treatments for NMS, it remains imperative to better understand, through clinical and preclinical studies, the neuropathology underlying these symptoms.

Animal models of PD cognitive deficits

As the cognitive impairment in PD patients became a relevant issue, the preclinical research started developing new tools suitable for the study of these deficits.

In particular, among the extended range of nonmotor, cognitive deficits appearing in PD patients mentioned above, several animal models have been recently validated for the study of spatial and discriminative memory, attention, and learning abilities related to the disease. Here we present a review of the best characterized and most widely used animal models of these PD symptoms in nonhuman primates and in rodents (for a more extensive essay, compare Fernagut and Chesselet 2004, Emborg 2007, Bezard and Przedborski 2010, Bovè and Perier 2012, and Porras et al. 2012).

Neurotoxin-based models

MPTP rodent models

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a highly lipophilic protoxin that, after crossing the blood-brain barrier (BBB), is converted by MAO-B to its active metabolite 1-methyl-4-

phenylpyridinium (MPP⁺) which, in turn, is taken up by the dopamine transporter (DAT) and damages dopaminergic neurons by oxidative stress (Beal 2001). MPTP can be systemically administered in mice, but must be locally injected into specific brain regions in rats. In the latter case the treatment can follow an acute regimen that produces ~90% striatal dopamine depletion and 70% dopamine neuron loss in the substantia nigra pars compacta (SNpc) and is stable for at least 7 d (Jackson-Lewis et al. 1995), or a subacute regimen that causes a more progressive neurodegeneration with ~40%–50% depletion of striatal dopamine and 30%–40% dopamine cell loss, which can be maintained up to 21 d (Tatton and Kish 1997).

This model is used to reproduce motor (Gerlach and Riederer 1996), as well as nonmotor, deficits (Fox et al. 2010) of PD. However, the occurrence of Lewy body formations following the administration of MPTP has been observed but not later confirmed (Fornai et al. 2005). Most important, it has been suggested that in MPTP-intoxicated animals, the dopaminergic fiber loss can spontaneously recover (Beal 2001), making this model difficult to use for longitudinal studies to assess progressive cognitive impairments.

Finally, MPTP is highly toxic to humans and thus has to be handled with extreme care (Dunnett and Lelos 2010).

MPTP nonhuman primate models

The use of nonhuman primates in PD research has a long history. In the first experiments, macaques were submitted to unilateral intracarotidian injection (Benazzouz et al. 1993), and successively to bilateral intoxication achieved with different regimens of systemic administration. In these studies, the ability of MPTP to affect neurotransmitters other than dopamine has been shown and related to the concomitant loss of noradrenaline and serotonin found in the brain of PD patients (Pifl et al. 1991).

Animal models based on the use of nonhuman primates certainly represent a crucial tool for the study of human diseases in general and of cognition in particular, due to their motor and cognitive skills as well as their neuroanatomical complexity closely resembling those of humans. However, economical and ethical considerations still limit the employment of monkeys in preclinical research.

6-OHDA rodent models

The most common animal model used in the PD preclinical research is based on the use of 6-hydroxydopamine (6-OHDA) (Ungerstedt et al. 1974). Due to its inability to cross the BBB, this neurotoxin needs to be injected directly into the target brain structure (Gerlach and Riederer 1996), where it binds receptor transporters and retrogradely kills the neurons by oxidative stress. Because of the structure similarity, 6-OHDA is taken up by terminals of catecholaminergic neurons at the side of injection. Thus, to selectively affect dopamine cells and better mimic PD dopaminergic degeneration, the toxin can be administered together with inhibitors of noradrenaline and serotonin transporters (e.g., desipramine and citalopram, respectively).

According to the protocol, 6-OHDA is administered into the SNpc, the medial forebrain bundle (MFB), or the striatum. The direct injection of the toxin into the SNpc or the MFB causes a fast and massive degeneration of dopaminergic cell bodies that therefore involves the nigrostriatal pathway according to an anterograde progression. Conversely, 6-OHDA injection into the striatum initially affects the dopaminergic terminals and thus damages the striatonigral pathway and the projecting structures according to a retrograde progression (Tadaiesky et al. 2008). Administration of 6-OHDA has been largely used to reproduce

the hemiparkinsonian rodent model for the study of the motor symptoms of the disease. In this case, the toxin is injected unilaterally at a concentration able to produce a midbrain dopaminergic degeneration of $\geq 80\%$ that, in turn, results in an asymmetric motor impairment resembling the akinesia of PD patients.

More recently, the use of 6-OHDA has been applied to the study of NMS of PD. In this case, some changes to the injection protocol are strongly suggested. First, the toxin should be injected bilaterally into the brain, in order to avoid the possible compensatory effect of the unlesioned hemisphere on the lesioned one on the behavioral performance. Notably, a bilateral symmetric dopamine depletion would prevent the confounding effect of an asymmetric motor output. Finally, since a bilateral massive ($\geq 80\%$) loss of dopaminergic neurons would cause a severe akinesia, if not animal death, the toxin, when bilaterally injected, has to be used at a lower concentration in order to obtain a partial ($\sim 65\%$) loss of dopaminergic neurons. Importantly, such modified protocol is not only more suitable for the study of cognitive NMS, but it also results in a model that resembles much more the parkinsonian condition. In fact, the onset of PD nonmotor symptoms is often at an early stage of the disease, when the motor repertoire is still preserved and the dopaminergic damage is $< 70\%$ (Gerlach and Riederer 1996).

Overall, the animal models based on 6-OHDA are very reproducible and widely used in PD research. On the other hand, it is worth noting that this type of lesion neither mimics the progressive dopaminergic degeneration characterizing PD in patients nor is it accompanied by the formation of Lewy bodies normally found in PD brains.

α -Synuclein genetic models

α -Synuclein is a 140-amino acid protein that represents the main component of Lewy bodies and Lewy neuritis. Postmortem studies in PD patients have shown that mutations of the gene coding for α -synuclein is related to an inherited form of the disease (Mouradian 2002), and increased expression of normal α -synuclein can increase the risk of developing PD in sporadic, nonfamilial cases.

The preclinical research commonly uses mouse models expressing genetic modification of the α -synuclein gene in order to unmask its role in PD. In this regard, many different lines of transgenic mice have been generated in the last 10 yr targeting different promoters (e.g., PDGF- β , Thy-1, TH promoter, prion promoter, and many others) to overexpress α -synuclein in its wild-type or mutated forms (for detailed review, see Fernagut and Chesselet 2004). In these studies behavioral and neuropathological alterations were consistently observed in the lines expressing the highest level of the transgene or the severity of the mutation.

The use of rodent models overexpressing α -synuclein to reproduce a selective nigrostriatal neurodegeneration requires the injection of viral vectors (primarily lentiviral and adeno-associated viral vectors) directly into the SNpc (Kirik and Bjorklund 2003). However, although conceptually promising, at present only a few preliminary data exist on viral-mediated α -synuclein overexpression in nonhuman primates. In one study, marmoset monkeys received two stereotaxic unilateral injections in the SNpc of adeno-associated virus that resulted in posture and motor head bias, which worsened consistently over time with an increase in α -synuclein expression (Kirik et al. 2003). In a subsequent study, marmoset monkeys were similarly injected with a different type of adeno-associated virus. The same symptoms appeared, but with a significant delay of almost 10–15 wk (Eslamboli et al. 2007). An attractive feature of this gene transfer model is that the use of adeno-associated viral vectors induces a progressive in-

crease in protein expression that takes several weeks to reach its peak, with the lesion developing over a similar period of time. However, it should be kept in mind that approaches based on stereotaxic injection of viral vectors do not reproduce the endogenous pattern of expression of α -synuclein in the brain, which is instead achieved by generating BAC transgenics with the full α -synuclein gene, including its own promoter (Hansen et al. 2013). Overall, although none of the available transgenic models fully recapitulates the human disease, nevertheless they may represent an important tool for the study of new antiparkinsonian drugs directly targeting specific PD-related genes.

Preclinical studies of cognitive deficits in PD

Whereas PD has been originally described as a motor disease, the concomitant occurrence of nonmotor cognitive deficits is now widely recognized. Consequently, the preclinical research is committed to develop new animal models to reproduce and investigate cognitive domains, such as attention, cognitive flexibility, planning, and problem solving, associated with an experimental parkinsonian condition. To this aim, the animal models described above are used to investigate the cognitive phenotype corresponding to an early, premotor stage of the disease. We describe below some of the most common behavioral tests used to evaluate the cognitive performance of nonhuman primate and rodent animal models. The studies here reported and the results obtained are also summarized in Table 1.

MPTP-based nonhuman primate model

Most of the cognitive deficits revealed in MPTP-treated monkeys not only mimic those observed in PD patients but also resemble those found in patients with frontal lobe damage.

Frontal lobes represent a complex integrative brain region that receives and sends projections to different areas and is involved in many cognitive and motor functions. It has been suggested that the cognitive impairment found in PD patients could arise, at least in part, from the abnormal functioning of the prefrontal cortex basal ganglia–thalamocortical circuit, rather than from a localized frontal cortex dopamine deficiency (Robbins and Arnsten 2009; Galvan and Smith 2011). In this context, the decisive role of the intralaminar thalamic nuclei in the transmission of salient sensory stimuli underlying attentional, rewarding, and reinforcing processes has been pointed out (Matsumoto et al. 2001; Minamimoto et al. 2005, 2009; Ding et al. 2010; Redgrave et al. 2010). These nuclei represent the main source of thalamic inputs to the striatum and regulate the striatocortical pathway via the activation of striatal projection neurons and cholinergic interneurons.

The object detour retrieval task (ODRT) is a behavioral test for monkeys that requires complex sequential motor planning and measures perseverative responses. The animal faces a transparent box with one open random side: The food present in the box can be grasped only if the box is entered from the correct side (i.e., making a detour). The task reproduces a conflict between the visual information of the reward located in front of the subject with the tactile information indicating a barrier. To correctly perform the task, the monkey has to inhibit the impulsive response of direct horizontal movement of the arm toward the food, and actively search the open side of the box. In this task, the “detour ability” of the animal is considered as an indirect measure of problem-solving skill that involves plastic reasoning necessary to change the spatial relation between itself and the objects through an active movement.

It has been shown that MPTP-intoxicated monkeys are slower in performing this task as the post-MPTP period progresses,

Table 1. Summary of the original articles reviewed: Each study is reported indicating the animal model employed and the test used to assess the cognitive impairment

Reference	Animal	Model	Test
Baunez and Robbins 1999	Lister rats	6-OHDA bilatDS	OTC
Bonito-Oliva et al. 2013	C57BL/6 mice	6-OHDA bilatDS	NOR
Braga et al. 2005	Wistar rats	MPTP BilatSNpc	T-Maze
Costa et al. 2012	Rats	6-OHDA MFB	Hole board test
Costa et al. 2012	C57BL/6S mice	TH-aSyn	Hole board test
Da Cunha et al. 2001	Wistar rats	MPTP bilatSNpc	AA
Da Cunha et al. 2003	Wistar rats	MPTP bilatSNpc	MWM
De Leonibus et al. 2007	CD1 mice	6-OHDA bilatDS	SOR–NOR
De Leonibus et al. 2009	CD1 mice	6-OHDA bilatDS	SOR–NOR
Decamp et al. 2004a	Cynomolgus monkey	MPTP systemic	VDR
Decamp et al. 2004b	Rhesus monkey	MPTP systemic	ASST
Decamp and Schneider 2006	Rhesus monkey	MPTP systemic	ASST
Decamp and Schneider 2009	Rhesus monkey	MPTP systemic	MDR
Dowd and Dunnett 2005	Rats	6-OHDA MFB or DS	OTC
Freichel et al. 2007	C57BL/6 mice	Thy1-aSyn	MWM–fear conditioning–AA
Gasbarri et al. 1996	Sprague-Dawley rats	6-OHDA bilatHIP	MWM
Gevaerd et al. 2001	Wistar rats	MPTP bilatSNpc	AA
Hsieh et al. 2010	Wistar rats	MPTP bilatSNpc	NOR 3
Magen et al. 2012	Mixed background mice	Thy1-aSyn	Y-Maze–SOR–NOR–OTC
Masliyah et al. 2011	Mixed background mice	PDGFB-aSyn	MWM
Millan et al. 2010	Rhesus monkey	MPTP systemic	VDR–ASST
Miyoshi et al. 2002	Wistar rats	MPTP bilatSNpc	MWM
Moriguchi et al. 2012	C57BL/6 mice	MPTP systemic	Y-Maze–NOR
Mura and Feldon 2003	Wistar rats	6-OHDA bilatMFB	MWM
Pothakos et al. 2009	C57BL/6 mice	MPTP-probencid	MWM
Schneider and Pope-Coleman 1995	Cynomolgus monkey	MPTP systemic	ODRT
Schneider et al. 1998	Cynomolgus monkey	MPTP systemic	ODRT
Schneider et al. 1999	Cynomolgus monkey	MPTP systemic	VDR
Schneider et al. 2003	Cynomolgus	MPTP systemic	VDR
Schneider et al. 2012	Cynomolgus monkey	MPTP systemic	VDR MDR
Tadaiesky et al. 2008	Wistar rats	6-OHDA bilatVLS	MWM
Tanila et al. 1998	C57BL/6 mice	MPTP systemic	T-Maze
Turle-Lorenzo et al. 2006	Wistar rats	6-OHDA bilatS	OTC
Sy et al. 2010	Wistar rat	MPTP BilatSNpc	NOR

(AA) Active avoidance; (ASST) attentional set-shifting; (MDR) modified delayed response; (MWM) Morris water maze; (NOR) novel object recognition; (ODRT) object detour retrieval task; (OTC) operant task conditioning; (SOR) spatial object recognition; (VDR) variable delayed response.

compared to controls, and normally show a higher number of wrong and perseverative responses (barrier reaching), increasing in consequence the task completion time (Schneider and Pope-Coleman 1995). Such a cognitive impairment is similar to that of monkeys with dorsolateral prefrontal cortex lesion, frontal lobe patients, and human infants younger than 1 yr old (Diamond and Goldman-Rakic 1989). However, neither L-DOPA nor the selective agonist of the nicotinic acetylcholine receptor (nAChR) SIB-1508Y alone could ameliorate the cognitive aspect of the performance, although the former could at least improve the motor impairment induced by the neurotoxin (Schneider et al. 1998). Nonetheless, when combined together, the two treatments could bring significant improvements in both cognitive and motor functions, leading the authors to hypothesize that this drug combination may address the dopamine deficiency of PD while also addressing the reduction in noradrenergic and cholinergic function characteristic of the disorder (Schneider et al. 1998).

In the variable delayed response (VDR) task, the monkey is placed in front of two wells, one containing food and the other empty, that it can observe for 2 sec, before an opaque screen is lowered in front of the animal. The two wells are then covered with identical sliding plates, and the screen is removed. The ability of the animal to choose and uncover the well containing food is evaluated. The task is performed with variable delay lengths up to 60

sec. Control subjects perform the task with a delay-dependent increase in errors, up to a chance level, reflecting the limits of their short-term spatial memory. In contrast, MPTP-treated monkeys poorly perform in this test, shifting from a delay-dependent to a delay-independent performance profile, producing the same kind of errors as the control subjects, regardless of the delay length (Schneider et al. 1999).

Although L-DOPA is unable to ameliorate the VDR performance (Schneider et al. 2012), nAChR agonists SIB-1508Y and SIB-1553A induced a long-lasting improvement in performance (Schneider et al. 1999, 2003). Coherent with this data, postmortem studies performed on MPTP-treated animals have shown that whereas cortical dopaminergic levels are intact, norepinephrine levels are reduced in both the cortex and the caudate nuclei. In this regard, it has been hypothesized that the rescue found following nAChR stimulation is mediated by the increase of norepinephrine release in these areas (Schneider 1990). Moreover, also S33138, a dopamine D₃ receptor antagonist, could improve the percentage of correct response for the shortest delay (Millan et al. 2010).

In order to better understand the cognitive nature of this deficit and to distinguish between the attentional and the working memory component involved in VDR tasks, a test variant with attentional cueing has been proposed. In this case, before the screen is lowered the examiner alerts the animal to the baiting of the well to ensure that the monkey pays attention to the wells. Interestingly, this protocol did not change control ani-

mals' score, but significantly improved the performance of MPTP-treated monkeys (Decamp et al. 2004a). An additional variant of VDR is the modified delayed response (MDR) task, in which the attentional demands of the task are manipulated to allow good performance in trials with low attentional load and impaired performance in trials with higher attentional load by increasing the length of time of cue presentation. Also in this case, the presence of the cue, as well as its duration, could improve the performance. Notably, L-DOPA administration, in a dosage that maximally improved parkinsonian motor symptoms, had a detrimental effect on the task performance, while SIB-1553A had, once again, a beneficial effect on it (Decamp and Schneider 2009, Schneider et al. 2012). Those studies demonstrated that the impaired performance in VDR task is mainly due to an attentional rather than a working memory deficit in this model.

The attentional set-shifting test (ASST) evaluates cognitive flexibility and set-shifting ability in monkeys. It is inspired by the Wisconsin Card Sorting Test (WCST), notoriously impaired in frontal lobe and PD patients (Downes et al. 1989; Owen et al. 1992). To perform this task, the animal is required to perform different subtests in which it must develop and maintain an appropriate response strategy across changing stimulus characteristics by shifting the attention focus among different aspects of the same object and adjust the behavioral response according to

subtest rules. MPTP-intoxicated monkeys were still able to perform all stages of the task with a normal overall response latency. However, with the exception of the simple discrimination, their performance was significantly impaired in all other subtests, with particular difficulty in the discrimination reversal and extra-dimensional shift (EDS) subtests, where they produced a bigger number of errors (i.e., were particularly unable to adjust the response accordingly to an altered feedback; Decamp et al. 2004b). As for VDR, the performance in this task is improved by the administration of the nAChR agonist SIB-1553A (Decamp and Schneider 2006). S33138, in this case, could ameliorate the primate performance in EDS (Millan et al. 2010); whereas its main site of action remains unclear, the authors suggest that it may be the dopamine D3 receptor-rich globus pallidus linked to associative basal nuclei circuits.

The attentional deficits and the reversal learning difficulties revealed by VDR, MDR, and ASST in this model of PD are coherent with the behavioral impairment found in early or nonmedicated PD patients (Lees and Smith 1983; Wright et al. 1990; Maddox et al. 1996).

6-OHDA- and MPTP-based rodent models

The use of PD rodent models obtained through the brain injection of 6-OHDA or MPTP represents a manageable, reproducible, and valid tool for the study of cognitive symptoms such as executive dysfunction, memory impairment, and visuospatial deficits (for a more extensive review on NMS in rodents, refer to Lindgren and Dunnett 2012).

The Morris water maze (MWM) is an extensively used behavioral test for the study of visuospatial memory in rodents. Indeed, in the early stages of PD, patients tend to show spatial memory impairment with a relative preservation of perceptive visuospatial and executive functions mainly due to striatal involvement (Pillon et al. 1997, 1998). However, as the disease progresses, multiple and severe spatial memory impairments appear (Owen et al. 1993). Thus, different versions of MWM seem to be ideal to model these types of deficit observed in patients.

Regardless of the version used, the MWM apparatus consists of a pool filled with opaque water and containing a platform. In the "cued version" of the task the platform is always visible and during the training phase the animal is guided toward it by a well-rendered cue on it. This protocol requires a short training phase. In the test phase, the latency to reach the platform is measured. In the most common "spatial version" the platform is submerged and the animals are trained for several days to find it by using, as spatial references, external cues placed around the pool. In the test phase, the platform is removed and the time spent by the animal in the area where the platform was is used as a measure of spatial learning; this version of MWM requires that the animal build a spatial representation that guides it toward the platform. Different from the "cued version," in the "spatial version" of the MWM the platform is always submerged and the only way to correctly perform the task is by using the distal cues surrounding the pool. The latency to reach the platform during the training session is usually adopted as a measure of the learning process, while the test performance is an index of the solidity of the acquired memory. The performance in the former protocol is mainly mediated by basal nuclei, while in the latter it is largely dependent on the hippocampus (McDonald and White 1994).

The selective involvement of these different brain structures in the two versions of the MWM is clear from the results of several studies. A selective lesion in the SNpc (Miyoshi et al. 2002; Da Cunha et al. 2003; Tadaiesky et al. 2008), which mainly projects to the striatum, or the systemic MPTP treatment (Pothakos et al. 2009) selectively impaired the learning process as well as the mem-

ory test performance of rodents in the cued, but not in the spatial, version of MWM. Those behavioral observations were accompanied by a reduction of dopamine levels in the striatum and prefrontal cortex, but not in the hippocampus (Miyoshi et al. 2002; Da Cunha et al. 2003). Conversely, the bilateral injection of 6-OHDA into the dorsal and ventral subiculum and adjacent CA1 hippocampus area (Gasbarri et al. 1996) selectively affected the test performance in the spatial, but not in the cued, version of MWM. Moreover, in the aforementioned study conducted by Da Cunha and colleagues, the otherwise normal performance in the spatial version of the test could be worsened by hippocampal injection of lidocaine (Da Cunha et al. 2003). In addition to these data obtained with pharmacological models of PD, transgenic mice expressing α -synuclein aggregates in the temporal cortex and the hippocampus (Freichel et al. 2007; Masliah et al. 2011) also showed deficits in the spatial protocol.

Interestingly, a bilateral injection of 6-OHDA into rats' MFB could impair the performance of the animals during learning and testing in both versions of MWM (Mura and Feldon 2003). Indeed, MFB includes projections from both SNpc and the ventral tegmental area; the latter is the origin of the meso-cortico-limbic dopaminergic pathway that projects also to the CA1. Moreover, Costa et al. (2012) have recently reported that rats unilaterally injected with 6-OHDA in the MFB showed a reduction of both spontaneous and stimulated dopamine release in the hippocampus. The behavioral analysis revealed in these animals' spatial memory impairment, as tested in the open field hole board, was reverted by L-DOPA treatment.

Novel object rRecognition (NOR) and spatial object recognition (SOR) are two memory tests frequently used to investigate attention, discrimination, and spatial memory in rodents. Both these tests measure the ability of the animal to detect a change in the object physical characteristics or in its spatial location, and rely on the natural attraction of rodents for the novelty. To correctly perform the tests, the animal has to pay attention to the environment and memorize the objects during a "familiarization" session. After a variable delay, the animal is required to remember the familiar object and discriminate it, during the test, from a new object (NOR), or detect the shifted position of a familiar object to a new location (SOR). The performance is evaluated on the base of the time spent by the animal exploring the new/relocated object over the total exploration time of the unchanged objects (Bevins and Besheer 2006).

Bilateral injection of MPTP in SNpc did not affect the basal exploration activity of rats, but resulted in impaired novelty discrimination during a short-delay NOR test (Sy et al. 2010). Post-mortem analysis revealed both hippocampal microglial activation and decreased density of pyramidal neurons in the CA1 area (Sy et al. 2010). These data are in agreement with microglial activation and increased levels of inflammatory cytokines observed in the SNpc, putamen, and hippocampus of PD patients (Sawada et al. 2006).

In a similar model, chronic administration of MK-801, a noncompetitive NMDA receptor antagonist, resulted in a mild improvement of the performance, accompanied by a partial recovery of dopaminergic transmission in SNpc and striatum (Hsieh et al. 2010). The authors suggest that the MPTP injection induces an excitotoxic release of glutamate in the striatum and a consequent neuroinflammatory response in the hippocampus, which is rich in NMDA receptors and mediates memory functions (Hsieh et al. 2010).

On the other hand, bilateral injections of 6-OHDA in the mouse striatum selectively impaired the performance in the long-term, but not in the short-term NOR test (Bonito-Oliva et al. 2013). In this study, the authors attributed the memory impairment to a deficient long-term potentiation in the dentate gyrus,

but not the CA1 area of the hippocampus. In fact, both the memory deficit and long-term plasticity were reverted by the administration of L-DOPA or the selective dopamine D1 receptor agonist SKF81297, but not the D2 receptor agonist pramipexole (Bonito-Oliva et al. 2013).

In another study, it has been shown that systemic administration of MPTP in mice produces a gradual impairment in the short-term NOR that correlates with the progressive impairment of long-term potentiation in the CA1 area of the hippocampus (Moriguchi et al. 2012). On the other hand, when tested for their spatial memory, mice injected with 6-OHDA in the striatum were impaired in both the short- and the long-term SOR, suggesting a predominant role of dopamine in modulating acquisition and maintenance of spatial information (De Leonibus et al. 2007). The same authors successively showed that this deficit is restored by the administration of the mGluR5 selective antagonist MPEP, suggesting the possibility of a presynaptic modulatory action of mGluR5 receptors on the dopamine release from the residual nerve terminals (De Leonibus et al. 2009). Thy1-aSyn transgenic mice fail in both short- and long-term SOR tests (Magen et al. 2012).

T-Maze and Y-Maze are two classic behavioral tests to measure reference and working memory in rodents. Despite the simple structure of the apparatus (Y or T shapes), different paradigms can be applied to study discrimination, and spontaneous and controlled alternation between the arms of the maze. Placed in the center, rodents explore the apparatus with the tendency to enter the arm visited less recently. Such spontaneous alternation is impaired in α -synuclein transgenic mice (Magen et al. 2012), but not in MPTP-treated mice (Moriguchi et al. 2012).

An alternative protocol is based on the controlled alternation between arm entries, achieved by rewarding one arm with the presence of food. The animal is trained to discriminate and memorize the goal (rewarded) arm that can be fixed or can alternatively change according to a criterion. Rats bilaterally injected in the SNpc with MPTP were able to perform the task when the reinforced arm was always the same, but were unable to learn the criterion in the alternate choice protocol (Braga et al. 2005). Similar findings are reported in MPTP-intoxicated mice impaired in the ability to acquire the criterion dependent on the duration of the delay between training and test (Tanila et al. 1998).

Active avoidance (AA) is a memory task based on associative and emotional learning. In AA, the animals are trained to associate the presentation of a specific cue with the subsequent occurrence of a negative event (shock) and to actively prevent the shock by moving to a different place in the apparatus. The learning is inferred by the number of correct responses to the cue presentation (escape and shock avoidance) and the response latency. Bilateral injection of MPTP in the SNpc in rats induces an impairment in this test (Da Cunha et al. 2001), partially reversible by caffeine (Gevaerd et al. 2001). Thy1-aSyn mice show an age-dependent deficit in this task, as well as in fear conditioning, likely to be due to the expression of α -synuclein aggregates in the amygdala (Freichel et al. 2007), a brain area known to mediate emotional processes. These data are in line with the presence of Lewy bodies and Lewy neurite deposits in the amygdala of PD patients (Braak et al. 1994), as well as the selective impairment in the recognition of facial emotion (Clark et al. 2008) and blunted reactivity during aversive/unpleasant events observed in these patients (Bowers et al. 2006).

The operant task conditioning (OTC) is a well-established behavioral task used to test cognitive impairment in several rodent models. Generally, the animal is trained to learn an operant behavior, aimed at receiving a reward or avoid a punishment. In the lateralized nose-poke task, the animal faces a wall with three holes surmounted by three lights: A sustained nose-poke in the

central hole triggers one of the lateral lights and food (reward) is provided from the hole ipsilateral (same version) to the light or, in a more complex protocol, opposite (opposite version) to it.

6-OHDA lesioned rats were impaired in the opposite task, with the worse deficit if the injection was in the MFB with respect to the striatum, showing a neglect related to the execution of a contralateral response rather than a sensory deficit (Dowd and Dunnett 2005). In a similar test, Thy1-aSyn transgenic mice showed an impairment in the reversal phase of the task (Magen et al. 2012) that required them to update reinforced motor action and switch to a new, reversed rule.

The operant task protocol can be manipulated in order to test the animal attention and motor response preparation. This is done by training rats with a bilateral striatal 6-OHDA lesion to press a lever and wait until a luminous cue guides them to the hole with food reward; when the interval was rendered unpredictable by random duration the lesioned animals were significantly impaired (Baunez and Robbins 1999). In a similar paradigm the lever had to be kept pressed until a light cue (of a random duration) was turned off in order to retrieve the food, the reaction time performance of lesioned rats was compromised by premature or delayed lever release (Turle-Lorenzo et al. 2006). Chronic treatment with L-DOPA or the dopaminergic D2-like receptor agonist piribedil allowed a rapid and full recovery. Thus OTC can highlight in rodents the reversal learning deficit and attention dysfunction already reported in MPTP-treated monkey.

Conclusions

The aim of this short review was to offer an overview on the state of the art of the research on the cognitive deficits associated with PD, as addressed by behavioral studies in rodents and nonhuman primates.

In the last few decades, the occurrence of nonmotor, cognitive symptoms in PD patients became an increasingly recognized issue. As a consequence, the preclinical research has generated a number of new animal models for the study of different aspects of the cognitive impairment associated with the disease.

Despite the limits of each of these models, it has been possible to precisely mimic several of the most important cognitive symptoms occurring in PD patients, such as impairment in executive functions in forms of novel, spatial, and discriminative memory, attention, and problem solving. Regardless of some discrepancies in the data obtained, probably due to the differences in the protocol adopted and in the animal strain employed, these animal models have been able to reproduce the cognitive deterioration observed in both early and late parkinsonian conditions. Moreover, these animal models also showed biochemical and electrophysiological dysfunctions in the same anatomical sites found in patients, such as the prefrontal cortex and the hippocampus. Since our understanding of the molecular and cellular mechanisms underlying the progressive loss of the executive functions in PD is still quite fragmented, the availability of faithful animal models will certainly allow a rapid comprehension of the neurobiological processes underlying cognitive NMS. Moreover, a clear pathophysiological characterization of the link between motor symptoms and cognitive deficits in PD will be a necessary step toward future therapies able to globally manage all aspects of the disease, a goal eventually to be achieved in the years to come.

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