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Review

Mouse Models of Cognitive Deficits Due to Alpha-Synuclein Pathology

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Abstract. Synucleopathies are neurodegenerative disorders characterized by abnormal accumulation of alpha–synuclein, most often in neurons. Familial forms are due to mutations or multiplications of the gene encoding for alpha-synuclein but most synucleopathies occur sporadically. They include Parkinson's disease (PD) and dementia with Lewy Bodies (DLB), which are both linked to cognitive decline. In DLB, dementia dominates the symptoms whereas in PD, subtle cognitive deficits are frequent and may appear even before motor symptoms, but only a fraction of patients develop severe dementia-type cognitive deficits. Several lines of mice were developed to model human synucleopathies by over-expressing the wild type or the mutated human alpha-synuclein under a variety of promoters. In addition, mice lacking alpha-synuclein have been used to determine the role of this protein in cognitive function. This chapter will review cognitive alterations observed in these models and discuss how they may help understand the various forms and stages of cognitive deficits observed in patients with synucleopathies.

Keywords: Cognition, memory, alpha-synuclein, Parkinson's disease, overexpression, promoter

INTRODUCTION

Alpha-synuclein (α-syn), a 140 amino acid protein encoded by the *SNCA* gene, is normally found in neurons throughout the brain and the peripheral nervous system. Three missense mutations (A30P and A53T, E46K) in the *SNCA* gene cause familial forms of Parkinson's disease (PD) [1–3]. Although not mutated in idiopathic PD cases, α-syn accumulates in Lewy bodies and Lewy neurites, which are key pathological features of the disease [4]. Moreover, duplication or triplication of the *SNCA* gene leads to PD, with a clear relationship between level of α-syn expression and age of onset of the disease [5, 6]. Interestingly, these genetic alterations in α-syn cause cognitive dysfunction: carriers of the E46K, A30P and A53T mutations displayed dementia and cognitive deficits [3, 7–9], and α-syn multiplications caused cognitive deficits in PD patients, whose frequency and severity were dependent on the number of gene copies [10–12]. Furthermore, α-syn duplication also caused cognitive deficits in healthy siblings of PD patients [13], and different haplotypes of the α-syn gene associated with risk for, or protection against PD differentially affected cognitive sequence learning [14]. Polymorphisms in the microtubule-associated protein tau (MAPT) were also strongly associated with dementia in PD [15]. Hence, it is not surprising that synucleopathies usually include cognitive deficits of variable severity. In PD mild cognitive deficits can appear in the pre-manifest stage of the disease, before any severe motor symptoms are observed. These deficits are primarily observed in the attentional and executive domains [16, 17]. As disease progresses, a subset of patients develops severe cognitive deficits leading to dementia [18, 19]. A main risk factor for the development of severe cognitive deficits in PD is age, but the presence of early cognitive deficits may also increase the risk of later, more severe, cognitive symptoms [20, 21]. The same is true for mutations in the glucocerebrosidase (GBA) or PRKN [22, 23] genes and for AD neuropathology like Aβ

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and tau [24]. In contrast to PD, dementia with Lewy bodies (DLB) is characterized by predominant early cognitive deficits, which are linked to the presence of extensive α-syn pathology in the cerebral cortex from an early stage of the disease [25]. In the majority of patients, these two synucleopathies can be differentiable from the clinical perspective, with predominance of dementia in DLB and of extrapyramidal symptoms in PD [26, 27]. Specifically, cases where extrapyramidal symptoms occur in succession with dementia are classified as DLB if dementia occurs within 12 months of parkinsonian features and as PD with dementia (PDD) if dementia occurs a year or more after the clinical diagnosis [26, 27]. However, it is still under debate whether DLB and PDD are neuropathologically distinguishable [26, 28]. Cognitive deficits are also present to a lesser extent in multiple system atrophy (MSA) [29], a disorder in which α-syn accumulates in oligodendrocytes rather than in neurons. Recently, a highly significant and negative correlation between the density of α-syn pathology and the Mini-mental state examination (MMSE) score that is used to screen cognitive impairments was demonstrated in a large cohort of patients that were diagnosed with different disorders characterized by Lewy body pathology (including DLB and PD) [30]. This suggests a possible causal relationship between the burden of α-syn pathology and cognitive deficits and highlights the importance of further exploring, using mouse models, the mechanisms downstream to α-syn pathology, which may cause cognitive deficits.

Numerous transgenic lines of mice overexpressing either wild type or mutated human α-syn in neurons or oligodendrocytes were created to mimic the pathological and clinical features of PD and other synucleopathies [31, 32]. Mice with α-syn deficiency, which are less relevant to the naturally occurring human disorders related to α-syn pathology, were also created, in order to study the role of this protein in molecular and cellular processes in neurons [33]. This chapter will review studies that have investigated the cognitive aspects associated with α-syn pathology induced in these various mouse models, excluding MSA models, for which there are no reports in the literature about cognitive deficits.

MOUSE MODELS OF ALPHA-SYNUCLEIN DEFICIENCY

In view of the clear involvement of α-syn in a number of human disorders that include cognitive deficits, it was of interest to determine whether or not α-syn plays a role in cognition. Indeed, even excess accumulation of a pathological protein can lead to loss of function by recruitment of the normal protein into pathological aggregates, as proposed for Huntington's disease [34]. A natural model was provided by a subpopulation of C57BL/6J mice previously used for cognitive studies, the C57BL/6JOlaHsd mice, that was discovered to carry a choromosomal deletion encompassing the SNCA gene encoding for α-syn [35]. This raised the possibility that differences in fear extinction between this line and the 6N line resulted from the absence of α-syn in the former line [36], but a comparison of fear extinction behavior between these lines and the B6Jax line that expresses α-syn ruled out an effect of α-syn expression on fear extinction [37]. This suggests that the differences found initially in fear extinction between the mouse strains C57BL/6JOlaHsd and 6N [36] are related to differences in the expression of other genes. Likewise, the similar performance of α-syn knock-out mice and wild type mice in the Morris water maze at 6 months of age ruled out the relation of α-syn deletion to cognitive function in this test, which was a potential concern regarding the interpretation of cognitive data obtained from C57BL/6JOlaHsd mice [38]. Other lines of mice deficient for α-syn were further created to rule out or confirm the involvement of this protein in cognitive function. Senior et al. have found that deletion of either alpha or gamma synuclein alone did not impair cognition, but deletion of both impaired cognitive function in the T-maze at 12–20 weeks [39]. Additionally, electrically-evoked striatal DA release was two-fold higher in the double-null mice than in either alpha or gamma synuclein deficient mice, with no change in striatal dopamine levels [39], consistent with previous reports of no change in dopamine levels following deletion of synucleins [40]. These results suggest that gamma synuclein may compensate for the absence of α-syn in regulating synaptic function, and thus may prevent cognitive decline in the α-syn deficient mice. These data support the hypothesis that cognitive deficits in synucleopathies are more likely related to a gain rather than a loss of α-syn function. Table 1 below summarizes the cognitive phenotype found in the different models of α-syn deficiency.

MICE OVER EXPRESSING HUMAN ALPHA-SYNUCLEIN

Many genetic models of Parkinson's disease are based on overexpression of either the mutated or the wild type human α-syn under various promoters. These models are summarized in details in our previous

Table 1
Lines of mice with alpha-synuclein deficiency

References	Genetic background	Neuropathology	Cognitive phenotype
Chen et al. (2002)	129/Ola backcrossed to C57BL/6	Not documented	No deficits in Morris water maze
Siegmund et al. (2005)	B6JOla B6N B6Jax	No change in DG	No differences in fear conditioning
Senior et al. (2008)	C57BL/6	↑ release of DA in STR	↓alternations in T-maze only when combined with gamma-synuclein deletion

DA, dopamine; DG, dentate gyrus; STR, striatum

review [31]. Most studies of these models focused on their motor deficits with less attention paid to their eventual cognitive deficits despite the frequency and severity of cognitive symptoms in human synucleopathies. We will first describe mice with predominant overexpression in the cerebral cortex, as they are more likely to model human pathologies in which cognitive deficits are early and severe as in DLB. Table 2 summarizes the various models of α-syn overexpression and the resulting pathological and cognitive alterations in these models.

Mouse models of predominant forebrain cortico/hippocampal-limbic α-syn pathology

Several lines of mice show extensive cortical α-syn pathology, which led the authors to conclude that these models reproduce DLB [41–45]. Nevertheless, it is important to mention that despite the predominant cortical pathology, nigral pathology also existed to some extent in the PDGF-β and CaMKIIα models, which could perhaps explain the impaired rotarod performance in these models [46, 47].

Mice overexpressing human wild type alpha-synuclein under the PDGF promoter

This line was the first published line of mice overexpressing human α-syn [46]. These mice displayed intraneuronal inclusions immunoreactive for α-syn and sometimes ubiquitin in regions typically affected in synucleopathies such as the neocortex, olfactory bulb, and to a lesser extent, midbrain [46]. Nevertheless, TH-positive terminals in the striatum, as well as striatal TH levels and activity were reduced in the line with the highest transgene expression [48]. Although further examination of this line also revealed a 25–50% decrease in striatal dopamine at 12 months of age and increased thigmotaxis [48], the extensive cortical pathology led the authors to state that this model more faithfully reproduces DLB than PD [41].

These mice did not show any loss of cholinergic neurons in the basal nucleus, a region that provides a major cholinergic projection to the cerebral cortex and has been linked to cognitive deficits [49]. In contrast, tests of hippocampal function such as the Morris water maze were impaired at 9 [50] but not 6 months of age [49]. This deficit could be related to a decrease in hippocampal neurogenesis [51] or to an upregulation of the metabotropic glutamate receptor (mGluR5) in the frontal cortex [50]. In accordance with these findings, MPEP, an mGluR5 antagonist, ameliorated the deficits in the Morris water maze [50]. Deficits in Morris water maze performance in the same line of mice at 12 months were associated with a decrease in both the post-synaptic densities and diameter of pre-synaptic terminals in the temporal cortex [52]. The number of neurons expressing α-syn in the neuropil and in the cell body also increased in the hippocampus and the neocortex of PDGF-aSyn mice, as well as the expression of markers of autophagy [52]. Passive immunization with an antibody against the C-terminus (CT) of α-syn was able to clear α-syn aggregates in PDGF-aSyn mice, restore pre-synaptic terminals diameter and post-synaptic densities, and ameliorate cognitive deficits at 12 months of age [52]. The results of these studies offer novel therapeutic approaches for synucleopathies and suggest that the associated cognitive deficits may be improved.

Mice overexpressing human A53T alpha-synuclein under the prion promoter

The A53T mutation causes a rare form of familial PD [1] and increases α-syn aggregation and pathology when expressed in mice under the mouse prion promoter, usually leading to more severe phenotypes than the wild-type form of the protein [53]. This line of mice displays a severe, even fatal, motor phenotype due to pathological alterations in motoneurons of the spinal cord [53]. In contrast to the clear motor phenotype, these mice were not cognitively impaired when tested in the Barnes Maze (a dry form of the

Table 2

Different models of alpha-synuclein overexpression, grouped by the promoters to induce transgene expression; the data in each model are further subgrouped by different lines of mice generated by different research groups, with the first reference referring to the originator of the line and followed by other groups using the same line in chronological order. The different models are ordered chronologically (by the year of the first report of the model), and so are the different lines within each model. 0–6 Months of age are considered "young age", 6–12 months "middle age", and over than 12 months "old age". In cases where two age ranges appear separated by a slash (e.g., young/middle), the onset was either in the borderline between two ranges or was reported in different age ranges by different groups using the same mice

References	Human syn	α-Promoter	Genetic background	Expression levels	Neuropathology	Cognitive dysfunction
Rockenstein et al. (2002) Fernagut et al. (2007) Fleming et al. (2008) Magen et al. (2010)	WT	Mu Thy-1	C57BL/6 × DBA2	2-3 fold of expression in WT	Young mice: I: SN, LC, other brain regions. No TH+ cell loss in SN or LC up to 18 m; Decreased cortical NE 7 m; decreased striatal TH and DA 14 m; decreased cortical ACh 6 m;	4-5 m: deficits in reversal learning (and reversal by L-DOPA), in novel object recognition, novel place recognition, 5-6 m, 7–9 m: deficits in Y-maze
Kahle et al. (2000) Freichel et al. (2007) Schell et al. (2009)	A30P	Mu Thy-1	C57BL/6	∼two fold of expression in WT	I: A, B, Cx, H, SC, SN, STR; B: TS amyloid staining; hyperphosphorylation of α-syn in cytosol in SC and phospho-Ser129 staining in A and Cx;	Old age onset: ↓ fear response (freezing and active avoidance), deficits in probe trial in Morris water maze
Zhou et al. (2008)	Y39C	Mu Thy-1	FVB/N	2.5-fold of expression in WT	Cx: I, phospho-Ser129 staining, ubiquitin+, apoptosis. No TH+ cell loss in SN	Old age onset: ↓ Morris water maze
Masliah et al. (2000) Masliah et al. (2001) Hashimoto et al. (2003) Winner et al. (2004) Price et al. (2010) Masliah et al. (2011)	WT	PDGF-β	C57BL/6 × DBA2	10–80% of human loading control	I in Cx, H, OB, and in TH+ cells in SN, ubiquitin+, glia+ in B, C, H, M, Th;↓ TH+ terminals and TH levels and activity in STR, ↓ DA levels in STR; No ChAT+ cell loss in NBM and STR up to 22 m; 6 m: Cx: ↑mGluR5 and colocalization of α-syn and mGluR5 4 m: ↓ Neurogenesis and ↑ apoptosis in DG ↓ post-synaptic density and pre-synaptic terminals diameter in Cx, ↑ markers of autophagy, ↑ number of α-syn expressing neurons in H and Cx, reversal by antibody against α-syn C-terminus	6 m: no impairments in Morris water maze, 9 m: ↓ Morris water maze, reversal by MPEP (mGluR5 antagonist). 12 m: ↑ thigmotaxis, ↓ Morris water maze, reversal by immunization against α-syn

Table 2
Continued

References	Human syn	α-Promoter	Genetic background	Expression levels	Neuropathology	Cognitive dysfunction
Giasson et al. (2002) Clinton et al. (2010)	A53T	Mouse prion	C57BL/C3H	∼5–30-fold of end. α-syn	I: B, C, SC, STR, Th; GFAP+ and gliosis in SC; altered neuronal morphology, diffuse accumulation of α-syn, Wallerian degeneration in ventral root of SC, axonal degeneration of sciatic nerve	Old age onset: ↓ Barnes circular maze
Nuber et al. (2008)	WT	CaM-tTA (tet-off)	C57BL/6	Less (≤90%) than human control; non significant increase (112%) only in Cx of CaM-αSyn mice. Highest expression in the forebrain—OB, Cx, and BG;	Trend to ↓ TH+ neurons in SN; ↓ DA in OB (reversed by ceasing gene expression); ↓neurogenesis in DG (reversed by ceasing gene expression)	Old age onset: ↓ retention in the Morris water maze
Lim et al. (2011)	WT, A53T	CaM-tTA (tet-off)	C57BL/6× B6C3H	Not documented	*A53T* 4–8 months: progressive dot-like α-syn pathology in H, MB, DG, Cg Cx, OB, S and STN; 8–20 months: progressive gliosis in MB; 12–20 months: progressive α-syn phosphorylation and ubiquitination in H and OB; α-syn phosphorylation in Cg Cx and ubiquitination in MB; 20–22 months: cytoplasmic α-syn accumulation and neuronal loss in Cx and H (pyramidal and granule cells). Synaptic structural defects and reversal by Dox which suppresses α-syn expression	A53T Middle age onset: ↓ contextual fear memory and reversal by Dox which suppresses α-syn expression; No change in cued fear memory

A, amygdala; ACh, acetylcholine; B, brainstem; BG, basal ganglia; C, cerebellum; CaM, calmodulin; Cg, cingulate; ChAT, choline acetyltransferase; Cx, cortex; DA, dopamine; DG, dentate gyrus; end. α-syn, endogenous levels of α-syn; GFAP, glial fibrillary acidic protein; H, hippocampus; I, inclusions; LC, locus coeruleus; M, midbrain; MB, mamillary bodies; mGluR5, metabotropic glutamate receptor 5; NBM, nucleus basalis of Meynert; NE, norepinephrine; OB, olfactory bulb; S, septum; SC, spinal cord; SN, substantia nigra; STN, subthalamic nucleus; STR, striatum; T, telencephalon; Tg, transgenic; Th, thalamus; TH, tyrosine hydroxylase; TS, thioflavine S; WT, wild-type.

Morris water maze); indeed number of errors and escape latency in retention trials or escape latency were not altered at most of the time points tested [54]. However, when triple transgenic mice that model Alzheimer's disease (AD) were crossed with these mice to model the Lewy body variant of AD (DLB-AD), the resulting mice displayed greater cognitive deficits at 6 and 9 months than the triple transgenics alone, suggesting an interaction between α-syn and beta-amyloid (Aβ) that may contribute to the enhanced cognitive phenotype [54].

Alpha-synuclein over expression under the CaMKinase promoter

The CaMKinase promoter confers high levels of expression in the forebrain, thus providing an ideal tool for generating models with predominant pathology in cortex and hippocampus, as in DLB, although the nigrostriatal system is affected as well as shown by the presence of dark cell degeneration in the substantia nigra pars compacta [47]. In a conditional model of wild type α-syn over expression under the CaM promoter, a reduced retention in the Morris water maze was found 7 days after a single probe trial, at 1 year of age. Neurodegeneration was found in the hippocampus of these mice at 20 months of age and neurogenesis in the hippocampus was already reduced at 24 weeks, perhaps leading to the cognitive phenotype. However, expression of the transgene can be turned off with doxycycline in these mice, which led to restoration of neurogenesis but cognitive improvement after dox treatment has not been tested yet. Thus a possible link between decreased neurogenesis, α-syn pathology, and cognitive deficits remains unclear [47].

Mice that conditionally expressed mutant A53T α-syn under the same promoter showed a progressive impairment of contextual fear memory from 4 to 8 months of age. This deficit was reversed by turning off transgene expression with doxycycline for 3 months, indicating that cognitive impairments depend on the transgene expression. Synaptic structural defects in the hippocampus, a brain region involved in contextual memory, were also reversed by turning off the transgene and were also progressive, becoming more severe from 8 to 12 months, further pointing to a link between α-syn expression, synaptic pathology in the hippocampus, and memory impairments [45]. A progressive gliosis was found in the mamillary bodies and other regions starting at 8 months of age and became more severe at 20 months of age. However, neuronal loss was found in the cortex and hippocampus only at 20–22 months, preceded by ubiquitination, phosphorylation and dot-like pathology of α-syn in those regions, suggesting that the memory impairments did not depend on neuronal loss but rather on α-syn associated synaptic failure [45].

Mice overexpressing mutated human alpha-synuclein under the Thy1 promoter

The α-syn overexpressing mouse that has so far been the most extensively studied for cognitive function is a transgenic line of mice expressing the A30P mutated human α-syn under the murine Thy-1 promoter, created by Kahle et al. [55]. At 12 months of age, these mice exhibited deficits in the probe trial of the Morris water maze that were not related to decreased swimming speed [42]. Impairments in fear-conditioning behavior were found at 17–20 months and were associated with distinct staining patterns of phosphorylated serine residue (phospho-serine-129 (PSer129)) [43], which is one of the features of neuropathological lesions in PD patients [56, 57]. Somal and nuclear PSer129 immunoreactivity increased with age in hippocampal and cortical areas as well as the lateral/basolateral amygdala nuclei and were also present in young, presymptomatic mice but not WT controls [43]. These mice further developed age-dependent, specific neuritic/terminal α-syn pathology in the medial parts of the central nucleus of the amygdala nucleus and one of its projection areas, the lateral hypothalamus. This suggests that α-syn becomes phosphorylated in distinct parts of the brain in this mouse model, showing age-dependent increases of nuclear PSer129 in cortical brain areas and the formation of neuritic/terminal PSer129 neuropathology within the fear-conditioning circuitry [43].

A line of transgenic mice overexpressing the human α-syn with the mutation Y39C under the Thy-1 promoter, showed cognitive impairments in the Morris water maze starting at 15–18 months and deteriorating at 21–24 months. This mutation is not observed in human patients but was used to enhance neurotoxicity by promoting protein aggregation. These mice widely expressed the mutant protein in the brain, including the cortex, hippocampus, striatum, thalamus, and substantia nigra, resulting in 2.5 fold higher level of expression than the wild type endogenous protein. At 24 months, transgenic mice developed neuropathology, such as α-syn and ubiquitin-positive inclusions, phosphorylation at Ser(129) of human α-syn, and increased apoptotic cell death in the cortex, which were not present at 18 months. Therefore, these pathological anomalies seem to follow the progression of cognitive dysfunction [44].

Mouse models of predominant brainstem cortico/subcortical-limbic α-syn pathology

Several lines of mice have been generated to reproduce the predominantly subcortical pathology associated with PD, which according to the Braak staging, starts in the olfactory bulb and ventral medulla, then progressively include raphe, locus coeruleus, and subsequently substantia nigra, basal nucleus of Meynert and amygdala, before invading the cerebral cortex at the latest stages of disease [58, 59]. As discussed earlier, this pattern of α-syn pathology is compatible with the progressive nature of cognitive deficits in PD, that consists of subtle impairments in executive function and attention at early stages of the disease [16, 17] and only evolve toward frank dementia at later stages in a subset of patients [18, 19]. Furthermore, the cognitive decline was found to correlate with the neuropathological stages of PD, suggesting that the risk to develop dementia increases with disease progression [60]. Although several lines of mice were generated to over-express α-syn specifically in catecholaminergic neurons under the tyrosine hydroxylase promoter, the cognitive function of these lines has not been characterized yet [61–65].

Mice overexpressing wild-type human alpha-synuclein under the Thy1 promoter

More recently, our laboratory has characterized the cognitive deficits of mice over-expressing human wild-type α-syn under the Thy1-promoter, generated in the laboratory of E. Masliah [41], with a focus on the early impairments that could correspond to cognitive deficits reported during the pre-manifest phase of PD [66, 67]. This mouse model of α-syn overexpression recapitulates most of the other non-motor symptoms typical to the preclinical stage of PD [31]. As PD patients display difficulties in reversal learning [66], Thy1-aSyn and WT mice were tested in a reversal learning task that assesses cognitive flexibility. Male Thy1-aSyn mice at 4–5 months of age learned a simple operant strategy as well as controls but showed greater difficulty than WT littermates in switching their responses at reversal, although they were eventually able to achieve criteria and learn the reversed contingency [68]. These mice also showed memory deficits in the novel object recognition (NOR) and novel place recognition tests at 4–5 months, and in the Y-maze test at 5–6 and 7–9 months. However, they showed no deficits in the cognitive aspects of the holeboard at 3–4 months, and in the Y-maze at 3–4 months and 11–13 months [69 and Magen et al. unpublished]. The latter observation is in agreement with previous evidence that deficits in Y-maze performance are associated with increased extracellular levels of dopamine [70]. Indeed the time course of increase in extracellular dopamine levels parallels that of the Y-maze performance as the earliest time point when dopamine was shown to be elevated in the striatum in Thy1-aSyn mice was 6 months while at older ages the hyperdopaminergic tone subsides, leading to loss of striatal dopamine by 14 months of age [71]. However, the deficits in the Y-maze and NOR test, both of which involve the cholinergic system [72, 73], also point to cholinergic deficits in the Thy1-aSyn mice. Human α-syn was indeed found to be expressed in cholinergic neurons in the basal nucleus and medial septum of Thy1-aSyn mice, which might have implications on the function of these neurons, and ACh levels decreased in the cortex of 6 month old Thy1-aSyn mice by 30% [Magen et al. unpublished], consistent with reports of degeneration of cortical cholinergic fibers in Thy1-[A30P]-aSyn mice at the same age [74].

CONCLUSION

In summary, although cognitive deficits have been less studied in mouse models of α-syn overexpression than motor function, a number of models have proven to show reliable deficits that can provide end-point measures to test new therapies for cognitive deficits in patients with synucleopathies. Like in humans with DLB, some models show predominant cortical and hippocampal pathology with associated deficits in hippocampal function. In these models, hippocampal dependent functions such as contextual fear memory and long-term spatial memory in the Morris water maze, as well as amygdalar functions like cued fear memory, were impaired beginning at middle or old age (8-9 months at the earliest) [42–45, 47, 50]. α-syn overexpression could also worsen associated amyloid pathology [54] and cognitive deficits could be reversed in some models by turning off the transgene [45]. In contrast, models with predominantly subcortical pathology more closely mimic the pathology seen in PD than in DLB, since the former is restricted to the brain stem in the early stages of the disease and only invades the cortex in the final stages [58, 59]. These models show early deficits at 4–6 months of age in a wide range of cognitive domains, such as short-term spatial working memory (Y-maze and novel place recognition tests), short-term non-spatial recognition memory (novel object recognition test) and cognitive flexibility (reversal learning) [68, 69, and Magen et al.

unpublished]. It is not known whether the cognitive domains affected in models with predominant subcortical pathology are also affected in models with predominant cortical pathology and vice versa, as Morris water maze was not used in the former models due to poor swimming ability of the mice, and on the other hand, the tests used in the Thy1-[WT]aSyn model were not reported to be used in other models. Therefore, one should not conclude that different types of cognitive deficits necessarily result from different regional patterns of α-syn pathology.

Three lines of mice in which the overexpression of α-syn was driven by the Thy1 promoter – Thy1-[WT] aSyn, Thy1-[A30P]aSyn and Thy1-[Y39C]aSyn – showed cognitive deficits, with variable age of onset, depending on the type of test used and whether the transgene overexpressed is wild type or mutant [42–44]. In the two latter lines, deficits progressed towards hippocampal involvement with deficits in the Morris water maze only at ages >12 months, compared to the earlier deficits in the WT aSyn model.

Although few mouse models develop the characteristic pathological finding of PD – dopaminergic cell loss in the substantia nigra – the presence of multiple deficits, including cognitive deficits in several lines of mice implicates an effect of the transgene on brain function at a relatively young age. Indeed, α-syn pathology and neurochemical changes were present in regions involved in cognition in a number of models, even though a direct causal link has not been demonstrated. The availability of multiple genetic models of synucleopathies provides a tool to investigate new neuroprotective therapies, and treatments specifically directed at cognitive dysfunction. Strategies found to improve cognition in models with predominant forebrain cortico/hippocampal-limbic pathology include turning off the transgene expression with doxycycline in conditional models [45, 47], or immunizing against the overexpressed α-syn protein [52], thereby preventing its aggregation and accumulation and the resulting downstream behavioral and neurochemical abnormalities. These strategies are particularly promising because they not only reverse cognitive deficits but also prevent their main potential cause. Other drugs target specific neurotransmitter systems and dysfunctional mechanisms resulting from α-syn accumulation, like the mGluR5 antagonist MPEP [50] and can be potentially employed for the treatment of cognitive deficits in DLB. In the α-syn models with predominant subcortical pathology, no treatment was used so far to reverse cognitive deficits. However, the early cognitive phenotype of the Thy1-aSyn model has only been characterized recently [69 and Magen et al. unpublished], and it is possible that novel therapeutic approaches currently under study may lead to the development of drugs for the early cognitive impairments in PD which, although mild, significantly affect the quality of life of patients and represent an unmet medical need in the treatment of the disease.

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