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REVIEW

Synucleinopathies: common features and hippocampal manifestations

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Abstract Parkinson's disease (PD), dementia with Lewy Bodies (DLB), and multiple system atrophy (MSA) are three major synucleinopathies characterized by α-synuclein-containing inclusions in the brains of patients. Because the cell types and brain structures that are affected vary markedly between the disorders, the patients have different clinical manifestations in addition to some overlapping symptoms, which are the basis for differential diagnosis. Cognitive impairment and depression associated with hippocampal dysfunction are frequently observed in these disorders. While various α-synuclein-containing inclusions are found in the hippocampal formation, increasing evidence supports that small α-synuclein aggregates or oligomers may be the real culprit, causing deficits in neurotransmission and neurogenesis in the hippocampus and related brain regions, which constitute the major mechanism for the hippocampal dysfunctions and associated neuropsychiatric manifestations in synucleinopathies.

Keywords Neuron · Oligodendrocyte · Glial cytoplasmic inclusions (GCIs) · Glial nuclear inclusions (GNIs) · Neuronal cytoplasmic inclusions (NCIs)

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Introduction

Synucleinopathies are a group of neurodegenerative disorders characterized by the formation of α-synuclein (α-syn)-containing inclusions in selective populations of neurons and/or glia. These disorders consist of Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and some other rarer disorders such as neurodegeneration with brain iron accumulation type 1 and other neuroaxonal dystrophies [1]. There are three major pathological forms of α-syn-containing inclusions associated with synucleinopathies. These consist of Lewy bodies (LBs) and Lewy neurites (LNs) found in neurons of patients with PD and DLB [2, 3], and glial cytoplasmic inclusions (GCIs) present in oligodendrocytes of patients with MSA [4]. Despite all these disorders have α-syn-containing inclusions deposited in the brain, the cell types and brain structures that are affected vary markedly between the disorders. This leads to different clinical manifestations, which are the basis for differential diagnosis. However, these disorders also present some shared symptoms such as chronic and progressive decline in motor, cognitive, behavioral, and autonomic functions [5].

In this review article, we concentrate on PD, DLB, and MSA, the three major synucleinopathies. We first compare the clinical features and pathological changes of these disorders. We then discuss how these disorders affect hippocampal functions, causing neuropsychiatric manifestations associated with hippocampal abnormalities.

Common features of the synucleinopathies

The synucleinopathies share some common features in both clinical manifestations and pathological changes. Clinically, they all present a chronic and progressive

decline in motor, cognitive, behavioral, and autonomic functions. Pathologically, they all have α-syn-containing intracellular inclusions, with LBs and LNs present in neurons of PD and DLB patients and GCIs in oligodendrocytes of MSA patients [1, 6, 7]. However, there are also subtle differences between these disorders in either clinical manifestations and pathological changes, which are the basis for differential diagnosis.

Clinical features

PD PD is one of the most common neurodegenerative diseases, affecting about 1.5% of people over the age of 65 years in Europe [8] with considerable worldwide variation in prevalence [9]. The cardinal clinical manifestations are motor symptoms, including bradykinesia, rigidity, rest tremor, and postural and gait impairments [10], by which PD is diagnosed. Based on the features of motor symptoms, PD can be classified into the tremor-dominant PD, which is relatively absent of other motor symptoms, and the non-tremor-dominant (akinetic/rigid) PD, which includes phenotypes described as akinetic-rigid syndrome and postural instability gait disorder. In addition, a subgroup of PD patients manifest as a mixed or an indeterminate phenotype with several motor symptoms of comparable severity [11, 12]. The tremor-dominant PD is often associated with a slower rate of progression and less functional disability than the non-tremor-dominant PD [13].

In addition to motor symptoms, PD patients also exhibit various non-motor symptoms. These include olfactory dysfunction, cognitive impairment, psychiatric symptoms (depression, visual hallucinations and anxiety), insomnia, rapid eye movement (REM) sleep disorder (RBD) [14], autonomic dysfunction (constipation, orthostatic hypotension, and urinary incontinence),Kibnd pain, and fatigue (Table 1). Some of the non-motor symptoms, such as impaired olfaction, constipation, depression, excessive daytime sleepiness, and RBD, occur before the onset of the motor symptoms [15]. Autonomic deficits preferentially occur in individuals with non-tremor-dominant PD subtype early in the disease [16, 17]. Although the non-motor symptoms are not used for disease diagnosis, they are important prognosis markers and subtype defining features [17].

DLB DLB is the second major synucleinopathy, accounting for around one in 25 dementia cases diagnosed in the community and one in 13 cases in secondary care. However, the true prevalence of DLB is likely to be much higher because its diagnosis is often missed, although there is evidence that new criteria aid case identification [18]. Clinically, DLB can be differentiated from PD with dementia (PDD) depending on the time that the dementia occurs. DLB is diagnosed when cognitive impairment precedes parkinsonism or begins within a year of parkinsonism. PDD is diagnosed when parkinsonism precedes cognitive impairment by more than 1 year [19]. Despite of refined diagnostic criteria for DLB, large autopsy studies indicate that DLB is often misdiagnosed in the clinical setting [20]. One of the reasons is that many older individuals have more than one neurodegenerative syndrome. For example, around one-half of DLB cases have visual hallucinations and RBD prior to or around the onset of memory loss [21–23]. In addition, around one-quarter of patients have anxiety and depression [22, 23]. Retrospective case–control studies have shown that a history of depression [24] or delirium [25] prior to the diagnosis of dementia is more common in DLB than in AD.

The motor symptoms in DLB are similar to those in PD and are usually assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) [26]. Compared to patients with PDD, patients with DLB have less asymmetry and resting tremor, a more rapid progression of motor symptoms and a poorer response to levodopa [19, 20, 27]. Moreover, DLB patients are particularly sensitive to developing extrapyramidal symptoms (EPS) and also to the potentially fatal complication of neuroleptic sensitivity, which affects approximately 50% of DLB patients [28]. In addition, gait abnormality and postural instability can be prominent in DLB [29] (Table 1).

Autonomic dysfunction is frequent in DLB and the severity is intermediate between those of MSA and PD. Most of patients with DLB have autonomic disorders, such as orthostatic hypotension, heat intolerability, dryness of cutaneous epithelium, mouth mucous membranes, and urination disorders [30].

MSA MSA is an adult-onset sporadic, progressive neurodegenerative disorder characterized by any combination of autonomic failure, parkinsonism, cerebellar ataxia [31]. The prevalence of MSA is 4.4 per 100,000 [32]. MSA, together with progressive supranuclear palsy (PSP), is called Parkinson Plus Syndrome. The Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) diagnostic criteria are consistent and valid. They can be used to distinguish MSA from PSP with high accuracy [33]. MSA is usually diagnosed based on clinical features (autonomic failure/urinary dysfunction plus either parkinsonism poorly responsive to levodopa or cerebellar ataxia) [34]. However, the accuracy of the clinical diagnosis of MSA is unsatisfactory due to the complexity of the clinical features and pathological changes, which sometimes overlap with those of other synucleinopathies [34]. The positive predictive value (PPV) at the later stage of MSA is reported to range from 60 to 90% [35]. A definite diagnosis relies on postmortem pathological examinations [36]. According to clinical features, MSA is subdivided into MSA-C, for those with predominant degeneration in

Table 1 Comparison of clinical features for PD, DLB and MSA

Rely on	Classification	Features	
PD Subtypes			
Age at Onset	YOPD (young(early)-onset PD) Aged 20-40 years	More often with rigidity and dystonia	
	[194]	Higher frequency of levodopa-related motor complications	
		≈1/3 represent PARK2-associated PD	
		Excellent response to levodopa	
		Slower progression of disease	
	LOPD(late(old)-onset PD)	Presented more often with the PIGD pattern	
	Aged >60 years	Rapid progression of disease	
	[194]	Lower frequency of levodopa-related motor complications	
Motor phenotype	Tremor-domainant PD	Good prognosis with slow progression	
	[194]	Essential tremor	
		Benign tremulous parkinsonism	
		Good response to levodopa	
		Wearing off	
		Increased fMRI activity in CTC circuitry	
		Degeneration in medial SN, ventral GPi, thalamic serotonin, and midbrain	
		"Eagle wing" configuration of DAT SPECT	
	Postural instability and gait dominant (PIGD) PD	Poor prognosis with rapid progression	
	[194]	Bradykinesia and rigidity	
		Dementia	
		Depression	
		Anosmia	
		Levodopa	
		Degeneration in ventrolateral SN	
		"Egg-shaped" configuration on DAT SPECT	
NMS-dominant phenotypic variants	Cognitive subtype	Older age (≥72 years)	
	[195–197]	Non-tremor-dominant motor phenotype associated with falls	
		Poor semantic fluency score (< 20)	
		Lower pentagon copying score (0<1<2)	
		Microtubule-associated protein tau (MAPT) H1/H1 genotype possibly a biomarker	
	Apathy subtype	High scores on apathy rating scales	
	[198]	Relatively severe motor symptoms	
		Concomitant depression	
		Lower cognitive	
		Fatigue and anhedonia	
		Response to dopaminergic drugs	
	Depression/Anxiety subtype [199, 200]	Anxious-depressed subtype	Younger age/Early age of onset
			Significant motor disability/higher UPDRS scores
			Postural instability/falls subtype
			Motor fluctuations
			Cognitive impairment
			Increased levels of anxiety and depression
		Depressed subtype	Older age/Late age of onset
			Shorter duration
			PIGD
			Significant motor impaiment
			High levels of depression
		Anxious subtype	Young age of onset
			Advanced disease with motor fluctuations
			PIGD
			Cognitive impairment
			High levels of anxiety

Table 1 continued

Rely on	Classification	Features
REM sleep behavior disorder subtype [201, 202]	Symmetric disease onset	
	Increased periods of freezing	
	Autonomic dysfunction	
	Prone to higher prevalence and severity of orthostatic symptoms	
	Higher rate of depression	
	Visual frequency of falls	
	Impairment of color vision	
	Impairment of color vision	
Lower limb pain subtype [203, 204]	Male > female	
	All age groups	
	Moderate to advanced PD	
	Pain in anterior proximal aspect of lower limb	
	Unrelated to non motor fluctuations	
	Responsive to opiates	
Olfactory subtype [205, 206]	A. Severe loss of olfaction (anosmia)	Dyskinesias
		Progressive weight loss
		Longer premotor disease duration
	B. Moderate loss of olfaction Urinary dysfunction	No further weight loss with disease progression
		Lower risk of dyskinesias
		Shorter premotor disease duration
Autonomic subtype	Urinary dysfunction [16]	Early noradrenergic deficit
		Postural hypotension
Dementia with Lewy body(DLB) subtypes		
DLB		Diagnostic specificity is high (mean, 92%), sensitivity is lower (mean, 49%) [207]
		Fluctuating impairments in attention, visual recognition and construction are more indicative of DLB [207]
		Lower tau deposition [117]
		28% frequency of GBA mutation [208]
		Male > female [209]
		No depression [210]
		Initially preserved memory function/cognitive fluctuations [211]
		Variable response to levodopa [1, 5]
MSA subtypes		
MSA-P		16%(Japan)-58%(Europe) of MSA cases [212, 213]
		Predominant parkinsonian syndrome [36]
		More frequent of cognitive impairment [214, 215]
		Less frequent of pyramidal signs [212]
		Autonomic clinical features [216, 217]
MSA-C		42% (Europe)-84% (Japan) of MSA cases
		Predominant cerebellar syndrome
		Less frequent of cognitive impairment
		More frequent of pyramidal signs
		Autonomic clinical features

cerebellar circuitry with ataxia, and MSA-P for those with predominant degeneration in the basal ganglia with parkinsonism [37, 38]. The MSA-P phenotype is the most common variant in Europe and USA, accounting for about 65% of all cases [39, 40, 41]. The most frequently occurring motor symptom in this phenotype is rigidity, followed by bradykinesia, tremor and postural instability [42]. Patients with this phenotype usually show poor response to levodopa. In Japanese population, MSA-C phenotype is present in 83.8% of MSA patients at first examination and in 48.6% of the patients at last follow-up [43]. These patients usually present ataxia of gait, instability, and falls but also with ataxia of limbs and speech, intention tremor, and disorders of extraocular movements such as square wave jerks, saccadic pursuit, nystagmus, overshoot or undershoot dysmetria, or slow pursuit (Table 1).

Like PD and DLB, MSA patients also develop various non-motor symptoms, with the most common one being the autonomic failure. The symptoms associated with the autonomic failure include orthostatic hypotension and urogenital disturbances such as increased frequency, enhanced urgency, incontinence and/or retention associated with male erectile dysfunction and female genital hyposensitivity [44]. Pyramidal signs such as Babinski signs, spasticity, hyperreflexia due to pyramidal tract degeneration are found in around half of the patients [45]. More than one-thirds of patients have sleep disorders and dementia [46]. The sleep disorder is accompanied by the specific sleep-related inspiratory stridor. The patterns of cognitive deficits are widely overlapped with those in other parkinsonian disorders [46].

Pathological features

PD Pathologically, PD is characterized by the loss of pigmented dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the formation of α-syn-containing inclusions in neuronal somata and neurites designated LBs and LNs, or collectively known as Lewy-related α-syn pathologies (LRP) [1, 6]. Although the motor symptoms of PD are attributed to the loss of dopaminergic neurons within the area of the substantia nigra pars compacta (SNpc) [1], neuronal loss is also found in many other brain regions, such as the ventral tegmental area (VTA), the locus coeruleus (LC), nucleus basalis of Meynert (NBM), pedunculopontine nucleus (PPN), raphe nucleus, dorsal motor nucleus of the vagus, amygdala, and hypothalamus [5, 47].

The distribution and progression of LRP in PD was first investigated by Braak and his colleagues [2], who proposed a staging scheme based on the topographical location of LRP in a large cohort [2], which has been improved by subsequent studies. According to Braak staging, LRP initially occur in the olfactory mucosa and enteric nervous system, travel into the brain via the vagal and olfactory nerves, and progress to particular brain structures in a predictable pattern [2, 47]. This pattern begins in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and olfactory bulb (stage one), ascending to the pontine tegmentum (stage two), midbrain (stage three), mesocortex and allocortex (stage 4), and finally culminating in widespread neocortical regions (Stages 5 and 6) [2, 47]. Prospective assessment of PD patients to autopsy reveals that the progression of LRP in typical cases (excluding early-onset cases) is consistent with Braak staging, where brainstem LRP dominates in those surviving to 5 years, by 13 years 50% of cases have a transitional distribution to limbic regions, and by 18 years all have at least this pathological phenotype [6]. It is thought that the earliest stages represent a preclinical disease phase in the absence of any motor disability [2]. The pattern and severity of LRP were found to be correlated with different clinical phenotypes. The more rapid disease course, along with higher amounts of pathological deposits and additional neuropathology, suggests an even faster rate of LRP deposition that appears to be linked to multiple pathologies in older-onset PD patients. These cases have similarities to those described below with a dementia dominant phenotype.

DLB The frequency and density of LRP in DLB patients have little difference from those in PD and PDD patients [48]. Compared with PD patients, the majority of DLB cases are found to have an advanced Braak stage, with cortical involvement [48]. In contrast, DLB patients have a less marked loss of the dopaminergic neurons in the substantia nigra and a relative lack of D2 receptor upregulation in the striatum [49]. In addition, many patients with DLB have substantial amyloid deposition in the striatum, hippocampus and cortex [1, 5, 50], much like the older-onset group of PD patients mentioned above. Coexisting LRP and AD pathology (Aβ and tau) is frequently found in DLB at postmortem [51, 52].

MSA The core pathological feature of all clinical subtypes of MSA is the presence of α-syn-positive glial cytoplasmic inclusions (GCIs) in oligodendroglia, which are widely observed throughout the brain [53]. Other α-syn-containing inclusions found in the brain of MSA patients include glial nuclear inclusions (GNIs), neuronal cytoplasmic inclusions (NCIs), neuronal nuclear inclusions (NNIs) [7]. Although neuronal loss and GCIs are key pathological findings in MSA, the severity of these lesions and their regional distribution can be highly variable, resulting in clinical heterogeneity. Pathologically, MSA cases were separated into those with predominately olivopontocerebellar (OPC) and striatonigral (StrN) involvement, corresponding to the clinical phenotypes of MSA-C and MSA-P. Historically, these pathological

variants were termed striatonigral degeneration (SND) [54] and olivopontocerebellar atrophy (OPCA) [55], respectively. An earlier study described two clinically diagnosed MSA-P cases with widespread GCIs and neuronal loss restricted to the substantia nigra and locus coeruleus; such cases are examples of pure SND and were coined "minimal change" MSA [56]. In all the cases described by Ozawa et al. [57, 58], neuronal loss was present in at least one StrN and OPC region, with no cases being "pure" SND or "pure" OPCA. A report has also reported that a case of "minimal change of OPCA", with neuronal loss being confined to OPC structures [59]. Like most sporadic neurodegenerative diseases, the strongest known risk factor for MSA is ageing. Therefore, it is not surprising that the pathological hallmarks of other age-associated disorders are sometimes found in conjunction with MSA, termed concomitant pathologies. In 94 of MSA cases from the UK, screening of the dorsal motor nucleus of the vagus and substantia nigra revealed the presence of LBs, the pathological hallmark of PD and DLB, in approximately 10% cases [57]. These studies suggest that LBs may represent an independent disease process in MSA, although a similar study in 50 cases of Japanese MSA reported no cases with LBs [58]. However, significant correlation was mainly observed between the frequency of GCIs and the severity of neuronal cell loss, and between these pathological changes and disease duration [57]. Grading systems have been proposed with cases assigned a separate severity grade between 0 and 3 for both MSA-P and MSA-C pathology, reflecting the considerable overlap between these subtypes [1].

Hippocampal manifestations

The hippocampus is a major component of the brain that plays important roles in the consolidation of new memory, emotional responses, navigation, and spatial orientation. It belongs to the limbic system and consists of several structures, including the dentate gyrus, the CA1-CA3 layers, and the subiculum [60]. The entorhinal cortex (EC), located in the parahippocampal gyrus, is considered to be part of the hippocampal region because it serves as the main "interface" between the hippocampus and other parts of the brain. The hippocampus is one of the most vulnerable brain regions affected by synucleinopathies, and the hippocampal dysfunction may cause various neuropsychiatric manifestations such as cognitive deficits, depression, anxiety, hyposmia, anhedonia, and psychosis, which have described above. In this section, we will discuss the pathological changes in the hippocampus and the possible mechanisms underlying the hippocampal dysfunctions associated with depression and cognitive deficits, the most frequently occurring symptoms observed in the three major synucleinopathies [61–67].

Pathological changes

Hippocampal atrophy

There is a controversy on the volume loss of the hippocampus in PD patients with normal cognition (PD-NC). Some studies described the volume loss of the hippocampus in PD-NC as compared with normal controls [68–71]. Some others reported the lack of difference in the hippocampal volume between PD-NC and normal controls [72, 73]. Different from PD-NC, PD patients with mild cognitive impairment (PD-MCI) and dementia (PDD) show a significant reduction in the hippocampal volume [68, 69, 71–77]. Patients with DLB also have a reduced hippocampal volume as those with PDD. However, this volume reduction is not significantly different between DLB and PDD, although it is smaller than that in AD [71, 78–82]. In patients with MSA, only the MSA-P phenotype was shown to have a reduction in the hippocampal volume as compared with control subjects [83–85].

There is a body of evidence suggesting the correlation between hippocampal volume loss and cognitive impairment in synucleinopathies. For example, memory impairment is an important feature of cognitive dysfunction in PD. It can be observed since early stages [86], is more pronounced in patients with visual hallucinations [87, 88] and predicts conversion to dementia [89]. The results that significant hippocampal volume loss is only observed in PD-MCI and PDD but not in PD-NC indicate the association between hippocampal volume loss and cognitive impairment. Direct evidence showing the relationship between hippocampal volume loss and cognitive impairment in PD patients has been obtained by volumetric magnetic resonance imaging [71, 90–92], which showed a pattern (control > PD > PDD > AD) of changes in the hippocampal volume. It is suggested that low hippocampal volume can be an important predictive factor for the progression from PD-NC to PD-MCI and also from PD-MCI to PDD [75]. Discriminant analysis and a receiver operating characteristics approach showed that mean cortical thickness and hippocampus volume have 80% accuracy in identifying PD patients with dementia [93]. In addition, white matter hyperintensity (WMH) is demonstrated to be an additional factor determining the progression of cognitive impairment in PD [75]. The finding that both hippocampal volume and WMH contribute to the development of cognitive impairment and dementia in PD is important as it would allow further studies to investigate

the mechanisms by which hippocampal volume and WMH act synergistically in PD dementia.

The DLB patients also show the correlation between hippocampal volume loss and cognitive decline. For example, voxel-based morphometry results showed that the right hippocampus and amygdala volume correlated with Visual Memory Test in DLB patients [82]. In a study with 3T T1-weighted imaging, DLB patients were shown to have milder hippocampal atrophy that was accompanied by preservation of the CA1 compared with AD patients. Among DLB subjects, CA1 was correlated with the Recent Memory Score of the Cambridge Cognitive Examination (CAMCOG) and Delayed Recall subscores of the The Hopkins Verbal Learning Test (HVLT) [94]. These findings highlight the promising role of hippocampal subfield volumetry, particularly that of the CA1, as a biomarker for the distinction between AD and DLB. Compared with pure DLB patients, the mixed DLB/AD patients displayed greater atrophy rates in the whole brain, temporoparietal cortices, hippocampus and amygdala, and ventricle expansion, similar to AD patients. In the DLB and DLB/AD patients, the atrophy rates correlated with Braak neurofibrillary tangle stage, cognitive decline, and progression of motor symptoms [95].

The MSA patients also manifest cognitive impairment, with prevalence rates being up to 31%. The patterns of cognitive deficits are widely overlapped with those of parkinsonian disorders, with some suggestive of hippocampal dysfunction [46, 96]. However, direct data showing the correlation between cognitive impairment and hippocampal atrophy in MSA remain to be collected.

It is well established that reduced hippocampal volumes are consistently associated with major depression [97–99]. Studies have shown that about 90% of PD patients have at least one neuropsychiatric symptom, among which, depression is considered as the frequent one. Studies with magnetic resonance imaging (MRI) detection have revealed that the patients with a history of several depressive episodes have significantly smaller hippocampal volumes in comparison to controls [100, 101]. This observation was further confirmed in meta-analyses of MRI studies of hippocampal volume in depression [102, 103]. Depression was also found in patients with DLB and MSA [104]. Since the hippocampal volume loss is also present in both diseases, it may also contribute to the depression, although studies for the direct link have not been reported.

Hippocampal α-syn pathology

Since α-syn-containing inclusions (LBs, LNs, GCIs, GNIs and NCIs) are hallmark pathologies of synucleinopathies, it is reasonable to assume that the presence and density of these protein inclusions in the hippocampus and related brain regions are associated with neuropsychiatric impairments in these disorders. Attempts have been made to relate cortical LBs and LNs with cognitive impairment in PD. It was demonstrated in demented PD patients that the densities of LBs, LNs, and LGs (Lewy grains) were significantly greater in amygdala, entorhinal cortex (EC), and sectors CA2/CA3 of the hippocampus, whereas middle frontal gyrus, sector CA1, and dentate gyrus were least affected [105]. In patients with a long disease duration where sufficient time for the slow accumulation of LRPs can occur, limbic and cortical LRPs correlates with the presence and severity of cognitive impairment in PD [106–110]. In a study performed on elderly PD patients in whom parkinsonism preceded cognitive decline by at least 3 years, Kövari and colleagues found that LB densities in the entorhinal and anterior cingulate cortex may predict cognitive deficits in PD. They suggested that LB formation in limbic areas may be crucial for the development of PD dementia [111]. Harding and Halliday indicated that high densities of parahippocampal LBs could separate demented from non-demented PD cases with high sensitivity and specificity [108]. In a study where α-syn, phosphorylated tau (phosphotau) and Aβ plaque pathology in PDD and DLB patients was assessed semi-quantitatively in four regions of the neocortex, the decline in cognition, assessed by Mini Mental State Examination, was found to correlate positively with the cortical α-syn load. Patients also had varying degrees of senile Aβ plaque and phosphor-tau pathology. Regression analyses pointed to a combined pathology (Aβ plaque plus phosphor-tau plus α-syn-positive features), particularly in the prefrontal cortex and temporal lobe neocortex with the superior and middle temporal gyrus being a major determining factor in the development of dementia. This study suggests that cognitive decline in LB dementia is not a consequence of α-syn-induced neurodegeneration alone, and senile plaque and phosphor-tau pathology also contribute to the overall deficits.

In typical MSA patients, the oligodendrocyte GCIs and GNIs are seldom observed in the hippocampus, although their presence in the temporal lobe has been reported in some rarer cases [85, 112, 113]. Atypical MSA (aMSA) is a term recently introduced by Aoki and his colleagues [114] to describe cases that show hallmark GCI pathological changes while clinically present with frontotemporal dementia (FTD) syndromes associated with frontotemporal lobar degeneration and severe limbic and cortical α-syn neuronal pathology [114]. Compared with typical MSA, the atypical MSA has significantly more neuronal inclusions in anteromedial temporal lobe and limbic structures (e.g., hippocampus and amygdala) [114]. However, if the increased neuronal inclusions correlate with the severity of cognitive deficit in MSA remains to be investigated.

While the above studies suggest an association between cortical LBs and cognitive impairment, other studies have not confirmed this assumption [115–117]. As have been stated, LB pathology may be a structural manifestation of a cytoprotective response or a failed cellular self-preservation mechanism to confine and eliminate cytotoxic proteins, and the real pathogenic form of α-syn is its aggregates and oligomers. For example, although incidental LB disease (iLBD) is often assumed to represent preclinical PD [29], in some PD patients, significant neurodegeneration and cellular dysfunction precedes LB pathology in the SNpc, challenging the pathogenic role of LB pathology in PD [30]. Studies using protein-fragment complementation assays have demonstrated that α-syn oligomers are associated with enhanced cytotoxicity in living cells, which can be rescued by Hsp70 in a process that reduces the formation of α-syn oligomers [118]. Other convictive evidence comes from a study on α-syn-overexpressing cells, showing that the toxicity of α-syn was alleviated by a single chain antibody (scFv) targeting the clearance of oligomeric but not monomeric α-syn [119]. The neurotoxicity of α-syn oligomers has also been demonstrated in animal models using mutant forms of α-syn with decreased capacity to form fibrils but increased propensity to form soluble oligomers [120]. In these animals, α-syn accumulation in the hippocampus was accompanied by cognitive deficits [121, 122]. In accordance with the findings in cells and animals, patients with parkinsonism (PD, DLB, and MSA) have increased levels of α-syn oligomers in the brain compared to those without parkinsonism or to healthy controls [123–126]. The above findings suggest a relationship between endogenous α-syn oligomers and neurodegeneration in synucleinopathies. To support this notion, neuropathological studies in a large series have confirmed that staging of LB pathology is barely applicable to cognitive impairment and dementia. Only a percentage of cases showed a relationship between cortical LBs and cognitive impairment and dementia [115], indicating that cortical LBs are not per se causative of dementia, but rather indicators of pathological α-syn aggregates. While the pathophysiology of the neurodegenerative process can hardly be explained by LBs, the clinical symptoms do indicate a degenerative process located at the presynapses resulting in a neurotransmitter deficiency. It was shown that 90% or even more of α-syn aggregates in DLB cases were located at the presynapses, which was shown as Proteinase K-resistant in distinct brain regions, including the hippocampus, temporal cortex and substantia nigra [127]. The PK-resistant α-syn aggregates were also found in the presynaptic nerve terminals in the hippocampus and temporal cortex in A53T α-syn transgenic mice [127]. To further support the neurotoxicity of insoluble α-syn aggregates, recent studies showed that perturbing normal α-syn repeat motifs, which occurs in α-syn mutations such as E46 K, promotes a conversion of α-syn from physiological tetramers into monomers [128]; this conversion decreases α-syn solubility and increases its aggregation and neurotoxicity [128]. By examining the insoluble α-syn aggregates-accumulated presynaptic sites in both transgenic mice [127] and PD brains, it was found that the dendritic spines were retracted, whereas the presynapses were relatively preserved, suggesting a neurotransmitter deprivation. These findings give rise to the notion that not only cell death but also α-syn aggregate-related synaptic dysfunction may cause clinical symptoms in synucleinopathies [129].

Other pathologies

DLB and PDD are characterized by the presence of α-syn-containing LBs and LNs. However, they also show variable degrees of AD pathology, such as senile plaques and neurofibrillary tangles, particularly in areas of the cortex associated with higher cognitive functions [108, 130]. Although the decline in cognition in both dementias was found to correlate positively with the cortical α-syn load, patients also had varying degrees of senile Aβ plaque and phosphor-tau pathology. Regression analyses pointed to a combined pathology (Aβ plaque plus phosphor-tau plus α-syn-positive features), particularly in the prefrontal cortex (BA9) and temporal lobe neocortex with the superior and middle temporal gyrus (BA21, 22), being a major determining factor in the development of dementia [131]. Thus, cognitive decline in Lewy body dementias is not a consequence of α-syn-induced neurodegeneration alone but senile plaque and phosphor-tau pathology also contribute to the overall deficits. In atypical MSA, except GCIs and NCIs, numerous Pick body-like inclusions in hippocampus and amygdala associated with neuronal loss and atrophy are the most specific features of atypical MSA [114].

Mechanisms underlying hippocampal dysfunctions in synucleinopathies

The hippocampal formation receives information from widely spread cortical and subcortical regions, and in turn sends signals through efferent nerves to many of the cortical regions as well as subcortical nuclei [132]. Previous studies have demonstrated impairments of the dopaminergic, serotonergic, cholinergic, and adrenergic neurons from the subcortical nuclei and their association with hippocampal dysfunction in patients with PD-MCI, PD-D, and DLB, which have been well reviewed elsewhere [133, 134]. Here, we will focus on recent progresses for the potential mechanisms underlying the deficits in synaptic

transmission and neurogenesis induced by α-syn abnormalities and discuss their possible roles for the hippocampus-mediated depression and cognitive deficits in synucleinopathies.

α-Syn-induced deficits in synaptic transmission

The connectivity between neurons in the brain depends on the number of synapses and their plasticity. The synaptic plasticity mainly refers to a persistent strengthening and weakening of the synaptic transmission efficacy. There is a body of evidence supporting that α-syn abnormalities can affect the efficacy of synaptic transmission by both the presynaptic and postsynaptic mechanisms. One way that α-syn affects synaptic transmission is to modulate neurotransmitter release. This effect is likely mediated by affecting the spatial organization of distinct synaptic vesicle pools within the presynaptic terminal, possibly via α-syn multimerization [135, 136] or by modulating intersynaptic vesicular dynamics [137]. α-Syn may exert its effect on synaptic vesicle recycling by its ability to bind membrane and potentiate SNARE-complex assembly [138, 139]. Another way that α-syn affects synaptic transmission is to modulate the trafficking and activity of neurotransmitter transporters, which serve to remove neurotransmitters from the synaptic cleft and reuptake the transmitters into cytosol from which they are sequestered into vesicles for storage and later release. The transporters found to be regulated by α-syn include dopamine, serotonin, and norepinephrine transporters [133]. In line with the results for the presynaptic impairments observed in experimental models, in vivo imaging studies on synaptic functions of the central nervous system provide compelling evidence for presynaptic neurotransmitter deficiencies in PD, PDD and DLB [140]. In addition to the presynaptic mechanisms, α-syn can also affect synaptic transmission by modulating the activity and expression of postsynaptic receptors. For example, extracellular α-syn oligomers have been shown to impair long-term potentiation by activating NMDA receptors [141, 142]. Besides, extracellular α-syn and overexpressed α-syn have been demonstrated to promote clathrin-mediated NMDA receptor endocytosis, leading to the reduction in the level of membrane NMDA receptors and the NMDA receptor-mediated Ca^{2+} influx upon stimulation [143, 144]. In accordance with the in vitro findings, α-syn transgenic mice showed reduced surface NMDA receptor levels and NR2A/NR2B subunit ratio in the hippocampus and altered hippocampus-related memory and long-term potentiation (LTP) [143, 145].

As have mentioned above, the connectivity between neurons depends on not only the synaptic plasticity but also the number of synapses. Loss of synapses has been observed in the frontal and temporal cortex as well as the hippocampus in patients with DLB, which correlates well with the cognitive impairment [146, 147]. Significant loss of presynaptic terminals are also demonstrated a few months after small α-syn aggregates begin to appear in the hippocampus of an α-syn overexpressing mouse model of DLB [148]. When the overexpressing transgene was switched off, the synapse loss was reversed, with a simultaneous clearance of the α-syn pathology, indicating a toxicity of the α-syn aggregates to the synapse. In line with the results obtained in animal models, in human LBD brains, the accumulation of protease K (PK)-resistant small α-syn aggregates can be observed at presynaptic terminals [129, 149, 150]. How might these α-syn aggregates or oligomers damage the synapse or cause synaptotoxicity? Based on the evidence obtained so far, several potential mechanisms are suggested. First, α-syn oligomers may directly change the permeability of the synaptic membrane by forming α-syn pores [151, 152] or inducing membrane thinning [153–155]. Second, α-syn oligomers may induce synaptotoxicity by damaging mitochondria [156], reducing synaptic proteins [157–159] or interfering with synaptic vesicle recycling [144, 160]. Third, in addition to acting on presynaptic terminals, α-syn oligomers may damage spine morphogenesis by affecting the function of NMDA receptors [141] since the latter plays an important role in spine morphogenesis [161]. Given the importance of NMDA receptors in synaptic signaling and spine morphogenesis, it is no surprise to find in human post-mortem tissue and numerous models of PD that spine densities are altered [161, 162].

Taken together, α-syn abnormalities can cause either the impairment of synaptic plasticity or the loss of synapses, leading to deficits in synaptic transmission. The toxic effect of α-syn on synaptic transmission can disrupt the connectivity between either the neurons within the hippocampus or the hippocampal neurons with those from the subcortical nuclei. This will impair hippocampal function, causing the hippocampus-mediated cognitive deficits and depression. It is well established that hippocampal LTP represents the major experimental model for the synaptic changes underlying learning and memory. It has been demonstrated that the LTP in the CA3/CA1 Schaffer collateral/commissural pathway of the hippocampus are affected by exogenously applied α-syn oligomers [141, 142]. Because the synaptic plasticity of this pathway is modulated by the mesolimbic dopaminergic neurons in the medial substantia nigra (A9 neurons) and nearby ventral tegmental area (A10 neurons) through dopamine D1/D5 receptors [163–166], deficits in synaptic transmission between the dopaminergic neurons and the hippocampal neurons will impair the hippocampal function. As the evidence for this, in mice transgenic for truncated α-syn (1–120), the hippocampal LTP was found to change, which was associated with an

impaired dopaminergic transmission and a decrease of NR2A/NR2B subunit ratio in synaptic NMDA receptors. Deficits in hippocampus-dependent learning were also found in this animal model. Interestingly, the dopamine precursor L-DOPA was able to restore the hippocampal synaptic potentiation via D1/D5 receptors and to ameliorate the cognitive deficit in the parkinsonian animals [143]. In consistent with the results of animal experiments, a single serial section study assessing the mesocortical A10 dopamine neurons proper revealed limited degeneration in the A10 dopamine cell groups in PD and PDD patients [167]. Despite this, in vivo imaging suggests a reduction in cortical dopamine in patients with PDD [168], indicating a functional rather than structural depletion of dopamine in the mesocortical system.

Except the dopaminergic innervation, the hippocampal formation also receives the serotonergic and noradrenergic projections from the raphe nucleus and locus coeruleus, the two nuclei that are vulnerable to α-syn pathology. Deficits in the serotonergic and noradrenergic innervation to the hippocampus have been reported in PD patients [169], which are believed to contribute to the development of dementia and depression. In BAC α-syn transgenic rat model, a serotonergic deficit in the hippocampus as defined by reduced levels of serotonin (5-HT) 1B receptor, decreased 5-HT neurotransmitter levels, and a loss of serotonergic nerve terminals innervating the DG/CA3 subfield were observed, while the number of serotonergic neurons in the raphe nuclei remained unchanged. Importantly, the BAC α-syn rats showed an early anxiety-like phenotype consisting of reduced exploratory behavior and feeding [170]. Decreased 5-HT1A receptor availability is found in limbic regions including the hippocampus in depressed PD patients [171, 172]. These findings are in agreement with post-mortem evidence and support the hypothesis that reductions in postsynaptic 5-HT1A receptors availability could be an underlying mechanism for the development of depression in PD [171]. In addition, preferential degeneration of noradrenergic terminals is reported in transgenic mice overexpressing mutant human A53T α-syn [173]. Moreover, α-syn has been demonstrated to attenuate the norepinephrine transporter activity and trafficking [174]. Therefore, there is also a possibility that α-syn abnormalities in the noradrenergic neurons of the locus coeruleus may also affect the hippocampal function.

α-Syn-induced deficits in hippocampal neurogenesis

Adult hippocampal neurogenesis occurs in a relatively limited area, the subgranular zone (SGZ) of the dentate gyrus (DG). There are numerous studies supporting the role of adult hippocampal neurogenesis in memory formation and emotion processing. For example, early studies specifically ablating adult hippocampal neurogenesis suggest the role of newly generated granule cells in memory formation [175–178], which are confirmed by recent advanced technologies such as conditional gene targeting, viral injection, and optogenetic approaches. Besides, reduced hippocampal neurogenesis has been observed in animal models and some patients with depression. There is evidence that antidepressant treatment can improve the adult hippocampal neurogenesis and the depression symptom [179–182]. Because postmortem analyses of adult neurogenesis are limited, direct investigation of alterations in adult hippocampal neurogenesis has been carried out in only a few samples of PD and DLB patients. These studies have revealed changes in some proteins in the patients that are implicated in adult hippocampal neurogenesis. For example, the number of cells positive for proliferating cell nuclear antigen (PCNA), epidermal growth factor (EGF) receptor, nestin, and 3-tubulin was found to reduce in the SGZ and the subventricular zone (SVZ) of PD patients when compared to controls [183]. In addition, a reduction of Musashi-positive cells within the hippocampal SVZ, subgranular layer (SGL) and ependymal cell layer (EPL) SVZ (representing neural stem and progenitor cells within this area) was noted in specimen of DLB [184]. The observed decrease in the SGV and SVZ proliferation of patients with LB disease is speculated to be a consequence of dopamine depletion [183].

In contrast to the limited amount of data and materials from human LB brains, many studies have been conducted in PD animal models, mainly in rodents. Studies on dopaminergic lesion models using 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have revealed a negative impact of dopaminergic deafferentation on neural progenitor cell (NPC) proliferation in SVZ, and dopaminergic stimulation increases proliferation in non-lesioned and lesioned rodents [183, 185, 186]. These results reinforce the speculation for the role of dopaminergic innervation in SVZ proliferation. In addition to lesioned PD models, adult neurogenesis has been studied in different transgenic mice that overexpress wild type or mutant α-syn. In these mice, neurogenetic deficits can be observed in the hippocampus [67, 170, 187–189]. Although there is possibility that impaired dopaminergic innervation may contribute to the hippocampal neurogenetic deficits since degeneration of dopaminergic neurons also occurs in these animals [187, 190], evidence obtained also supports the direct effect of α-syn on neurogenesis. For example, in a tetracycline-suppressive (tet-off) transgenic mouse model, reduced neurogenesis in the hippocampus and olfactory bulb was observed when the A30P mutant α-syn was overexpressed, which was restored to control levels after the A30P α-syn was abrogated [191, 192]. In addition, the

induced pluripotent stem cells that derived from PD patients with SNCA gene triplication exhibited elevated α-syn expression and impaired neuronal differentiation and maturation [193], further supporting that the abnormal accumulation of α-syn may directly affect the neurogenesis in the hippocampus.

Due to the potential roles of adult hippocampal neurogenesis in memory formation and emotion processing, its defect may contribute to the manifestations of neuropsychiatric impairments such as cognitive deficits and depression in synucleinopathies.

Concluding remarks

While all the three synucleinopathies (PD, DLB, MSA) have α-syn-containing inclusions found in the brains of patients, the cell types and structures affected vary between different disorders. This determines the distinctive clinical features of each disease, although they all manifest as a chronic and progressive decline in motor, cognitive, behavioral, and autonomic functions. The formation of α-syn-containing inclusions is frequently observed in the hippocampus and related brain regions of patients with synucleinopathies, which are accompanied by hippocampal atrophy and dysfunction as well as neuropsychiatric symptoms such as cognitive deficits and depression. Although the α-syn-containing inclusions are hallmark pathological changes in synucleinopathies, increasing evidence supports that small α-syn aggregates or oligomers are toxic species that induce neurodegeneration initially starting at the synaptic site. Both neuronal functional change and degeneration in the hippocampus and some subcortical neurons with projections to the hippocampus and related regions can lead to the manifestations of neuropsychiatric abnormalities in synucleinopathies.

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