Journal of Neural Transmission (2022) 129:187–206
https://doi.org/10.1007/s00702-022-02467-8

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Fluid markers of synapse degeneration in synucleinopathies

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Received: 3 December 2021 / Accepted: 20 January 2022 / Published online: 11 February 2022

Abstract
The abnormal accumulation of α-synuclein in the brain is a common feature of Parkinson's disease (PD), PD dementia (PDD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA), and synucleinopathies that present with overlapping but distinct clinical symptoms that include motor and cognitive deficits. Synapse degeneration is the crucial neuropathological event in these synucleinopathies and the neuropathological correlate of connectome dysfunction. The cognitive and motor deficits resulting from the connectome dysfunction are currently measured by scalar systems that are limited in their sensitivity and largely subjective. Ideally, a marker of synapse degeneration would correlate with measures of cognitive or motor impairment, and could therefore be used as a more objective, surrogate biomarker of the core clinical features of these diseases. Furthermore, an objective surrogate biomarker that can detect and monitor the progression of synapse degeneration would improve patient management and clinical trial design, and could provide a measure of therapeutic response. Here, we review the published findings relating to candidate biomarkers of synapse degeneration in PD, PDD, DLB, and MSA patient-derived biofluids and discuss the findings in the context of the mechanisms associated with α-synuclein-mediated synapse degeneration. Understanding these mechanisms is essential not only for discovery of biomarkers, but also to improve our understanding of the earliest changes in disease pathogenesis of synucleinopathies.

Keywords Synucleinopathy · Parkinson's disease · Dementia with Lewy bodies · Multiple system atrophy · Biomarker · Synapse

Introduction

The term synucleinopathy refers to a group of adult-onset, progressive neurodegenerative diseases characterized by abnormal accumulation of α-synuclein in the brain (Spillantini et al. 1997; Baba et al. 1998; Jellinger 2003). The most prevalent diseases with underlying synucleinopathy include Parkinson's disease (PD), Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Neuropathological evaluation of these patients post-mortem reveals α-synuclein inclusions that can be found in neuronal cytoplasm (Lewy bodies), neurites (Lewy neurites), or in glial cytoplasm (glial cytoplasmic inclusions). Although synucleinopathy is common to these diseases, inclusion type and deposition pattern and degree of neuronal loss, as well as the temporal order and prevalence of clinical manifestations can differ substantially across synucleinopathies (see Box 2).

In the healthy brain, α-synuclein is expressed predominantly at presynaptic terminals (Iwai et al. 1995; Maroteaux et al. 1988) where it modulates neurotransmitter release (Burre et al. 2010). In synucleinopathies, α-synuclein exists in a thermodynamic equilibrium of soluble oligomers and insoluble fibrils (Baba et al. 1998; Jellinger 2003; Fusco et al. 2018) that can be propagated from neuron to neuron and from neuron to astrocytes (Hoffmann et al. 2016; Sorrentino et al. 2019; George et al. 2019; Olanow et al. 2019). It is increasingly recognized that the diffusible oligomeric assemblies, rather than the fibrillar form, are the driving factor underlying neurodegeneration, ultimately leading to connectome dysfunction and neuronal death (Mahul-Mellier et al. 2020; Bellucci et al. 2016). Studies using neuroimaging tracers of synaptic

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proteins reinforce the idea that synucleinopathies are a result of functional connectome deficits (Box 2).

Aggregation and propagation of α-synuclein at synapses are a major event in the pathogenesis of synucleinopathies (Calo et al. 2016), and may be exacerbated by activation of microglial cells (Hoffmann et al. 2016), which in turn induce the spread of α-synuclein pathology (George et al. 2019; Olanow et al. 2019). In addition, soluble α-synuclein can be transported from neurons into neighbouring astrocytes in response to stress and/or neurodegeneration (Sorrentino et al. 2019). The correlation between the spread of Lewy bodies and disease progression (Braak et al. 2003) suggests that synaptic propagation of α-synuclein is integral to disease pathogenesis.

Dopaminergic neurons of the substantia nigra are particularly vulnerable to synuclein pathology. Their extensive axonal projections (which can exceed 4 m in length) and abundance of synaptic contacts (estimated 1 million synapses per neuron) may make this neuronal population particularly susceptible to disruptions in energy (Pissadaki and Bolam 2013). It is this disruption of dopamine homeostasis in basal ganglia circuits (Bellucci et al. 2016; Lowther et al. 2014) and sensory–motor networks (Peraza et al. 2014) that underlies the motor symptoms that are a common feature of the synucleinopathies (Box 2). Non-motor symptoms on the other hand likely reflect progressive connective dysfunction in mesolimbic–striatal loops (Luo et al. 2014) or in visual and attentional, default mode, salience, and executive networks (Sourty et al. 2016; Lowther et al. 2014). The recurrent complex visual hallucinations that are prevalent in PD may be due to functional changes associated with GABA-ergic neurons in the primary visual cortex (Khundakar et al. 2016). Treatment of patients with the dopamine precursor, levodopa, or with dopamine agonists improves clinical symptoms, but does not modify or stop disease progression.

In summary, PD, PDD, DLB, and MSA are a result of functional connectome deficits induced by oligomeric α-synuclein at the synapse. Despite the clear evidence implicating synapse degeneration as an early event in synucleinopathy, there are currently no biomarkers of synapse degeneration that are established in the clinical routine. In this paper, we will first outline the need for synaptic biomarkers in synucleinopathies and discuss the use of α-synuclein species as synaptic biomarkers. We then review the current literature on biofluid markers of synapse degeneration in clinical cohorts of PD, DLB, and MSA patients, with a particular emphasis on placing the findings in the context the pathophysiological mechanisms of synapse degeneration that have been associated with α-synuclein. We will also discuss their potential added value in aiding the diagnosis of synucleinopathy-related diseases.

Box 1: core clinical and neuropathologic features of the most prevalent diseases related to synucleinopathy

Core neuropathologic features

PD PDD, and DLB

Moderate-to-severe neuronal loss in the pars compacta of the substantia nigra and Lewy bodies/Lewy neurites with an olfactory bulb only, brainstem-predominant, limbic predominant, brainstem/limbic, or neocortical distribution (Dickson et al. 2009; Beach et al. 2009). Distinguishing DLB, PD, and PDD requires clinical assessment.

MSA

Widespread neuronal degeneration and glial cytoplasmic inclusions throughout the white matter, with high abundance in the basal ganglia, substantia nigra, pontine nuclei, medulla, and cerebellum. Lewy bodies are present in rare cases (Trojanowski and Revesz 2007; Ubhi et al. 2011).

Core clinical features

PD

Motor parkinsonism (bradykinesia plus rest tremor or rigidity) is essential for a PD diagnosis. Non-motor manifestations such as dementia, depression, psychosis, and sleep disturbance are also prevalent (Postuma et al. 2015).

PDD

PD can cause a condition called PD dementia (PDD), which is clinically defined by a diagnosis of PD, with global impairment of cognition in more than one cognitive domain, sufficient to impair daily life, and where parkinsonian signs precede the development of dementia (Vasconcellos and Pereira 2015).

DLB

Dementia, typified by cognitive fluctuations in attention, executive function and visuoperceptual ability, and memory

domains, is essential for DLB diagnosis. Other core features include visual hallucinations, REM sleep disorder, and motor parkinsonism (McKeith et al. 2017). In contrast to PD dementia, in DLB, dementia precedes parkinsonism.

MSA

Core clinical features include autonomic failure, urogenital dysfunction, motor parkinsonism or a cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction), corticospinal disorders, and cognitive deficits (Gilman et al. 2008).

Box 2: neuroimaging tracers as measures of synapse pathology in vivo

For research purposes, positron emission tomography (PET) with the [^{11}C]UCB-J tracer can be used to quantify the density of the universal presynaptic vesicle protein, SV2A, and can provide valuable insight into the underlying synaptic pathology of an individual in vivo.

PD

Studies using [^{11}C]UCB-J have confirmed a decreased synaptic density in the substantia nigra of PD patients compared to healthy controls (Delva et al. 2020; Matuskey et al. 2020; Andersen et al. 2021). Reduced synaptic density in the red nucleus and locus coeruleus of PD patients has also been reported but was not replicated across studies. The SV2A tracer did not correlate with motor or nonmotor scores in PD patients.

DLB/PDD

In contrast to PD, a study using [^{11}C]UCB-J in a pooled set of patients with DLB or PDD revealed a more widespread reduction in synaptic density, not only in the substantia nigra but in all 11 cortical regions except for the hippocampus and amygdala (Andersen et al. 2021). Furthermore, synaptic density in the middle frontal gyrus correlated with executive function. A similar finding was reported in a small study of 2 DLB patients (Nicastro et al. 2020).

MSA

We found no published studies using this PET tracer in MSA patients.

Need for synaptic biomarkers in synucleinopathies

Cognitive and motor deficits are currently measured by scalar systems that are limited in their sensitivity and can be subjective. As the neuropathological correlate of underlying connectome deficits, synapse density is a good predictor of the rate of cognitive decline in synucleinopathies (Bereczki et al. 2016). Therefore, a marker of synapse degeneration could represent a much needed objective, surrogate biomarker of the core clinical features of these diseases.

There is also a need for a synaptic biomarker in the clinical trial setting. There are currently no therapeutic interventions that can slow down or stop diseases associated with synucleinopathy. Although several clinical trials are on-going, such treatments could be futile if delivered after irreversible neuronal damage has already taken hold. Successful future clinical trials require robust and specific biomarkers that can detect and monitor early disease pathogenesis, such as synapse degeneration.

To address this need, both neuroimaging and biofluid markers of synapse degeneration have been investigated. It is important to note, however, that while the neuroimaging SV2A PET tracer informs on the synaptic density at the point of analysis, it does not necessarily indicate an active degeneration of synapses. Quantification of synaptic proteins in the cerebrospinal fluid (CSF), on the other hand, may reflect the active clearance (or lack of, due to synaptic internalization or aggregation in the parenchyma) of synaptic proteins from the brain interstitia. Consequently, both neuroimaging and biofluid markers can provide complementary information as to the cumulative and active effects of a toxic (or therapeutic) agent on the synapse, respectively. As the costs for wide implementation of neuroimaging tracers are high and the use of radioactive tracers precludes PET use in certain patients/centres, biofluid markers have a wider clinical potential.

As synapse degeneration is common to all neurodegenerative diseases, a synaptic biomarker may not be specific to any one disease. This should not be seen as a limitation of synaptic biomarkers. After all, this is also the case for biomarkers of neurodegeneration. Alternatively, a synaptic biomarker may reflect dysfunction of a specific mechanism or degeneration of a specific synaptic subpopulation and therefore may be better suited to a specific disease or neuropathological subtype. For this reason, here, we first

focus on understanding the candidate synaptic biomarkers in terms of the biological mechanisms associated with these proteins and their source synaptic populations and later will discuss their utility in aiding clinical and differential diagnoses.

α-Synuclein species as biofluid markers of synapse degeneration in synucleinopathies

Both normal and pathological α-synuclein species play an important role at the synapse. As such, α-synuclein species could be considered a candidate biomarker of synapse degeneration. Different α-synuclein species (total and aggregated) have been studied in the CSF of PD and DLB patients. The majority of studies report a decrease in total α-synuclein concentration in the CSF of PD and DLB patients compared to healthy controls (Eusebi et al. 2017; Sako et al. 2014; Gao et al. 2015; Zhou et al. 2015; van Steenoven et al. 2018) with considerable overlap in CSF concentrations between PD and other synucleinopathies (Wennstrom et al. 2013; Backstrom et al. 2015; Magdalinou et al. 2015). Longitudinal studies found no change in CSF α-synuclein over 12 months in PD patients (Mollenhauer et al. 2016, 2017). The aggregated form of α-synuclein has been detected in the CSF of PD and DLB patients by real-time quaking-induced conversion (RT–QuIC) and protein misfolding cyclic amplification (PMCA) assays (Fairfoul et al. 2016; Shahnawaz et al. 2017; Quadalti et al. 2021). In contrast to total α-synuclein, several studies have shown that aggregated α-synuclein and phosphorylated α-synuclein are elevated in PD and DLB patients compared to controls (Eusebi et al. 2017; Zhou et al. 2015; van Steenoven et al. 2018). Initial studies reported that combination with other biomarkers was needed to show good diagnostic accuracy for PD, DLB, and MSA (Eusebi et al. 2017; Parnetti et al. 2014; Singer et al. 2020). More recently, studies are reporting a high sensitivity and specificity of CSF aggregated α-synuclein for PD and DLB, and to a lesser extent in MSA patients (Poggiolini et al. 2021; Rossi et al. 2021; Bongianni et al. 2019). In addition to its clinical utility, aggregated α-synuclein has been proposed as a promising biomarker to use in clinical trials that target α-synuclein pathology to stratify patients according to their α-synuclein aggregation profile (Brockmann et al. 2021).

These findings support alterations in CSF concentrations across synucleinopathies with good diagnostic accuracy, particularly in PD and DLB. While synuclein species may also prove to be useful surrogate markers of synapse degeneration in other neurodegenerative diseases (Oeckl et al. 2020), they may not be the most appropriate synaptic marker in patients with underling synucleinopathy where oligomerization, fibrillization, and sequestration of α-synuclein in the brain would impact on CSF concentrations. This may also be pertinent in clinical trials targeting synuclein pathology, where there is a need for an alternative surrogate measure of cognitive performance, independent of the drug target.

Biofluid markers of synapse degeneration in synucleinopathies

In this section, we review the literature on synaptic proteins, other than α-synuclein, in biofluids of patients diagnosed with any of the major synucleinopathies, namely PD, PDD, DLB, and MSA. We searched for studies in CSF and blood (plasma and serum). For the purposes of this review, we defined a protein as synaptic if it is included in the expert curated evidence-based database of synapse function and gene enrichment studies (Koopmans et al. 2019). We have only included biomarker studies that used quantitative methods (e.g., quantitative mass spectrometry or immunoassay) and, to improve diagnostic certainty, we only included that studies that used consensus diagnostic criteria or where neuropathological evaluation confirmed the diagnosis. We found 1 study reporting free concentrations of synaptic proteins in serum, 1 study of extracellular vesicles (EVs) in serum, and 17 studies in CSF. Table 1 summarizes the sample sizes and diagnostic criteria for each study as well as the principal findings for each synaptic protein including correlation to cognitive performance and motor scales. The functions of these synaptic proteins can all be related to mechanisms that are known to be associated with synuclein pathology, which provided a framework within which to discuss the findings. We first introduce the mechanism of synapse degeneration and its relationship to α-synuclein pathology and subsequently discuss the published findings of the candidate synaptic biomarker associated with this mechanism. A schematic representation of the mechanisms and associated candidate biomarker profiles in CSF is shown in the Fig. 1A–E. The numbers in parentheses in the text refer to corresponding process represented in Fig. 1.

Disturbances in vesicular-mediated neurotransmitter transport and secretion (Fig. 1A)

One of the normal physiological functions of α-synuclein is in vesicle-mediated neurotransmitter transport and secretion for which soluble *n*-ethylmaleimide sensitive factor attachment protein receptors (SNAREs) are fundamental to exocytosis and neurotransmitter release via synaptic vesicle recycling (Sauvola and Littleton 2021). In vitro studies have

Table 1 Studies of synaptic proteins in PD, PD dementia, DLB and MSA CSF, and serum EVs

Protein	Cohort (study)	Synucleinopathies							Other ND	
		Dx criteria	*n*	Direction of change				Correlation with cognitive/motor scales	Direction of change *n*	
			HC	PD	PDD	DLB	MSA			
A. Deficits in vesicle-mediated transport and secretory pathways										
i. Serum EVs										
SNAP25	(Agliardi et al. 2021)	1	40	=32				No correlation with cognitive or motor scales		
STX-1A	(Agliardi et al. 2021)	1	40	↓32				No correlation with cognitive or motor scales		
VAMP-2	(Agliardi et al. 2021)	1	40	↓32				No correlation with cognitive or motor scales		
ii. Blood										
β-synuclein	(Oeckl et al. 2020)	2–4	33		=13[a]	=13[a]			↑AD52 ↑CJD25	
iii. CSF										
SNAP25	(Bereczki et al. 2017)	5	87	↑52				No correlation with cognition or PD scales		
β-synuclein	(Oeckl et al. 2016)	2–4	36	=21	=15	=10				
	(Oeckl et al. 2020)	2–4	43	=25	=13[a]	=13[a]			↑AD151 ↑CJD23	
	(Halbgebauer et al. 2020)	4	66	=46					↑AD52 ↑CJD25	
GAP-43	(Sjogren et al. 2000)	6	32	23↓						
	PD (Remnestal et al. 2016)	5	114	=90[f]				↓ PD rating scale	↑AD43	
	DLB (Remnestal et al. 2016)	7	26			=[g]18			=[g]AD28	
	(Sandelius et al. 2019)	2,8	43	=28	=15	=27		↓global cognition in total dataset[c]	↑AD275 ↑lvPPA10	
DNM1	(Enache et al. 2020)[b]	2,4,9	29[d]		↑18	↑27		No correlation with cognition	↑AD24	
VGF	(van Steenoven et al. 2019)	9	22			↓44				
	1 (van Steenoven et al. 2020)	2,9	20			↓20		↓global cognition in total dataset[c]		
	2 (van Steenoven et al. 2020)	2,9	13			↓17				
	3A (van Steenoven et al. 2020)	4	–	↓109					↓AD20 ↓FTD20	
	3B (van Steenoven et al. 2020)	2,9	28			↓48				
SCG2	1 (van Steenoven et al. 2020)	2,9	20			↓20		↓global cognition in total dataset[c]		
	2 (van Steenoven et al. 2020)	2,9	13			↓17				
	3A (van Steenoven et al. 2020)	4	–	↓109					↓AD20 ↓FTD20	
PDYN	1 (van Steenoven et al. 2020)	2,9	20			↓20		↓global cognition in in total dataset[c]		
	2 (van Steenoven et al. 2020)	2,9	13			↓17				
	3A (van Steenoven et al. 2020)	4	–	↓109					↓AD20 ↓FTD20	
B. Deficits in synaptic plasticity										
Ng	(Wellington et al. 2016)	4,10	19	=31		=13	=29		↑AD100	
	(Janelidze et al. 2016)	11				=[e]47			↑AD74 ↓VaD34 ↓FTD33	
	PD (Remnestal et al. 2016)	5	114	=90[f]						
	DLB (Remnestal et al. 2016)	7	26			=[g]18			=[g]AD28	
	(Bereczki et al. 2017)	5	87	↑[b]52				↓global cognition in PD		
	(Selnes et al. 2017)	5	26	↓30				↓recall, attention, verbal fluency, motor in PD		
	(Portelius et al. 2018)	2	75	=37	=29	=33		No correlation with cognition	↑AD397 ↓ALS68 ↓bvFTD46	
	(Hall et al. 2020)	2,3,8,12	47	↓157	=29	=11	↓26	No correlation with cognitive or motor scales	↑AD124 ↓PSP21	

Table 1 (continued)

Protein	Cohort (study)	Synucleinopathies							Other ND
		Dx criteria	*n* HC	Direction of change PD	PDD	DLB	MSA	Correlation with cognitive/motor scales	Direction of change *n*
C. Synapse adhesion									
CNTN-1	(Chatterjee et al. 2020)	2,4	40[d]	↓58		=72		No correlation with cognitive or motor scales	
CNTN-2	(Chatterjee et al. 2020)	2,4	40[d]	=58		=72		No correlation with cognition or motor scales	
D. Excitatory/inhibitory dyshomeostasis									
NPTX2	(Boiten et al. 2020)	9	27[d]			↓48		↓global cognition in DLB	↓AD20
	1 (van Steenoven et al. 2020)	2,9	20			↓20		↓global cognition in total dataset[c]	
	2 (van Steenoven et al. 2020)	2,9	13			↓17			
	3A (van Steenoven et al. 2020)	4	–	↓109					↓AD20 ↓FTD20
	3B (van Steenoven et al. 2020)	2,9	28			↓48			
NPTXR	1 (van Steenoven et al. 2020)	2,9	20			↓20		↓global cognition in total dataset[c]	
	2 (van Steenoven et al. 2020)	2,9	13			↓17			
	3A (van Steenoven et al. 2020)	4	–	↓109					↓AD20 ↓FTD20
GluA3	(Enache et al. 2020)	2,4,9	29[d]		=18	=27			↑AD24
E. Altered metal ion homeostasis									
ZNT3	(Enache et al. 2020)	2,4,9	29[d]		=18	↑27		No correlation with cognition	↑AD24

The diagnostic (Dx) criteria and number of controls are shown for each study. The reported direction of change compared to controls (↑↓) and number of patients is shown for each synaptic protein in PD, PD dementia (PDD), DLB and MSA CSF, and serum EVs where reported p value was <0.05 compared to controls. Where reported p was >0.05, = is shown. Direction of reported significant ($p<0.05$) correlations (↑; direct, ↓; inverse) between CSF concentrations of the synaptic protein with cognitive performance or motor scales. Where available, direction of change for other neurodegenerative diseases compared to controls is also shown

ND neurodegenerative diseases, *AD* Alzheimer's disease, *CJD* Creutzfeldt-Jakob disease, *lvPPA* logopenic variant primary progressive aphasia, *FTD* frontotemporal dementia, *VaD* vascular dementia, *ALS* amyotrophic lateral sclerosis, *PSP* progressive supranuclear palsy

[a]Pooled PDD and DLB ,[b]Drug naive patients only, [c]As analyses were not stratified by diagnosis, it is not possible to extricate the effect of diagnosis on this correlation, [d]Subjective cognitive decline, [e]Includes PDD, [f]Untreated and treated PD, [g]Postmortem CSF

[1](Postuma et al. 2015), [2](McKeith et al. 2005), [3](Emre 2003), [4](Hughes et al. 1992), [5](Berardelli et al. 2013), [6](Wallin et al. 1999), [7](Hyman et al. 2012), [8](Gelb et al. 1999), [9](McKeith et al. 2017), [10](McKeith et al. 1996), [11](Geser et al. 2005), [12](Gilman et al. 1998)

demonstrated that α-synuclein can bind directly to the SNARE protein, VAMP-2, forming a bridge between the membrane and synaptic vesicle, which facilitates SNARE complex formation and stabilizes the docked vesicle, thus allowing the exocytosis of neurotransmitters (Lou et al. 2017). An interaction between α-synuclein and the actin cytoskeleton further regulates vesicle-mediated trafficking and vesicle pool organisation (Jeannotte and Sidhu 2008; Rust and Maritzen 2015).

Human and animal studies show that disruptions to vesicle-mediated trafficking and secretory pathways are a key feature of synucleinopathy, with downstream effects on neurotransmitter signalling. For example, neuropathological evaluation of PDD and DLB patient brains post-mortem has revealed reduced neuropeptide levels as well as reduced expression of SNARE proteins, the neurosecretory peptide VGF, and proteins such as dynamin-1 (DNM1), that are critical for vesicle fission and control SNARE formation (**1**) (Alpadi et al. 2013; Anantharam et al. 2012; Fernandez et al. 1996; Bereczki et al. 2016) (Cocco et al. 2010; Vallortigara et al. 2014). The implication of this latter finding to disease pathogenesis is highlighted by the correlation between DNM1 expression post-mortem with the rate of global cognitive decline in DLB and PDD patients (Vallortigara et al. 2014). As SNARE proteins are abundant in Lewy bodies and glial cytoplasmic inclusions isolated from DLB and MSA patients (McCormack et al. 2019), it has even been proposed that vesicle-mediated transport may serve to selectively target aggregated α-synuclein to the Lewy body inclusions (**2**). These studies are supported by PD mouse models, which show defects in synaptic vesicle recycling and redistribution of SNARE proteins in the striatum (Garcia-Reitbock et al. 2010; Nemani et al. 2010). Evidence that these defects are related to alterations in dopamine neurotransmission comes from the finding that levodopa treatment in these models

reversed the decrease in concentration of peptide neurotransmitters, such as dynorphin (Broderick et al. 2017).

These disruptions to neurotransmitter secretion maybe related to, or further exacerbated by, the disruption of actin cytoskeleton dynamics mediated by pathological α-synuclein (**3**) that has been observed in cells lines expressing α-synuclein harbouring mutations associated with familial PD (Sousa et al. 2009; Prots et al. 2018).

On the other hand, proteins such as β-synuclein and growth-associated protein-43 (GAP-43) may protect neurons against neurotoxicity by regulating and potentiating dopamine release at synaptic vesicles. For example, mouse models have shown that β-synuclein (**4**) can ameliorate motor deficits by inhibiting α-synuclein aggregation (Hashimoto et al. 2001) and potentiating vesicular monoamine transporter-2–dependent uptake of dopamine by synaptic vesicles (Ninkina et al. 2021). Whether alterations in β-synuclein expression and function are directly implicated in synucleinopathies has yet to be fully determined, but reduced β-synuclein expression has been reported across the cortex in DLB patients post-mortem with neuropathological confirmation of Lewy body pathology (Beyer et al. 2010) and a genetic study has reported two amino acid alterations in the β-synuclein gene of DLB patients. GAP-43 (**5**), a protein that regulates actin dynamics and induces axonal sprouting (He et al. 1997), can be sorted onto vesicles and transported down the axon by fast axonal transport to the growth cone or presynaptic membrane (Gonzalo and Linder 1998) where it has been implicated in dopamine release (Denny 2006; Dekker et al. 1989). Phosphorylation of GAP-43 by protein kinase C (PKC) facilitates synaptic vesicle recycling and neurotransmitter release via a direct interaction with vesicle proteins, SNAP-25, and synaptophysin (Holahan 2017). However, GAP-43 was nominally reduced in the brain of PDD patients post-mortem compared to controls (Bereczki et al. 2018), suggesting that altered GAP-43 expression may be a feature of synucleinopathy.

SNARE proteins

The principal components of the SNARE complex are synaptosomal-associated protein 25 (SNAP-25), the syntaxins 1A and 1B, syntaxin-binding protein-1, and the vesicle-associated membrane proteins (VAMP-1, VAMP-2) (Sevlever et al. 2015). Despite the growing evidence implicating vesicle-mediated transport in synuclein-mediated degeneration, a few studies have investigated the biofluid profile of the SNAREs in synucleinopathy-related diseases. Low concentrations of syntaxin-1A and VAMP-2, but not SNAP-25, have been reported in EVs isolated from the serum of PD patients compared to healthy controls (Fig. 1A, Table 1 Ai), thus supporting the idea that vesicle-mediated trafficking is impaired in PD (Agliardi et al. 2021). However, as shown in Table 1 Ai, the authors did not find any correlation between concentration of syntaxin-1A, VAMP-2, or SNAP-25 with age-at-onset, disease duration, tremor-dominant manifestation, postural instability/gait difficulty, levodopa dose, or cognitive score. Thus, a relationship between these potential biomarkers and cognitive and motor symptoms has yet to be established.

To our knowledge, CSF concentrations of VAMP and syntaxin proteins have yet to be investigated in synucleinopathies. On the other hand, one study has reported higher CSF SNAP-25 concentration in PD patients compared to controls (Fig. 1A, Table 1 Aiii), particularly in patients treated with levodopa (Bereczki et al. 2017). It is unclear whether this is due to the medication itself or whether it reflects the later disease stage of the treated compared to the untreated group. CSF SNAP-25 did not correlate with cognitive score or disease progression (Table 1 Aiii). The authors proposed that the increase in SNAP-25 in PD CSF reflects the continuous leakage of proteins into the brain interstitial fluid and subsequent clearance into the CSF due to on-going synapse degeneration.

β-Synuclein

β-Synuclein has been quantified in both serum (Table 1 Aii) and CSF (Fig. 1A, Table 1 Aiii) by targeted mass spectrometry (Oeckl et al. 2016, 2020). In both fluids, β-synuclein concentrations were comparable to controls in PD, and a pooled set of PDD/DLB patients. The same authors have since developed an ELISA assay for β-synuclein, which was used to successfully replicate the findings in CSF (Halbgebauer et al. 2020). In contrast to the synucleinopathies, β-synuclein may have utility as a synaptic biomarker in Alzheimer's disease and Creutzfeldt–Jakob disease (Oeckl et al. 2016, 2020). These findings suggest that biofluid concentrations of β-synuclein may reflect amyloid rather than synuclein-mediated synaptotoxicity.

GAP-43

A few studies have investigated GAP-43 as a candidate biomarker in synucleinopathies and results have been conflicting (Fig. 1A, Table 1 Aiii). One study reported specifically decreased CSF concentrations of GAP-43 in PD patients compared to controls, a reduction that was not apparent in other neurodegenerative diseases (Sjogren et al. 2000) and was not replicated in two subsequent studies (Remnestal et al. 2016; Sandelius et al. 2019). However, one of the latter studies did report a weak negative correlation between CSF GAP-43 concentration and disease severity in the PD group (Table 1 Aiii), suggesting that low CSF GAP-43 concentrations may be a feature of advanced PD (Remnestal et al. 2016). Those same studies also reported no change in CSF GAP-43 concentration between DLB patients and controls.

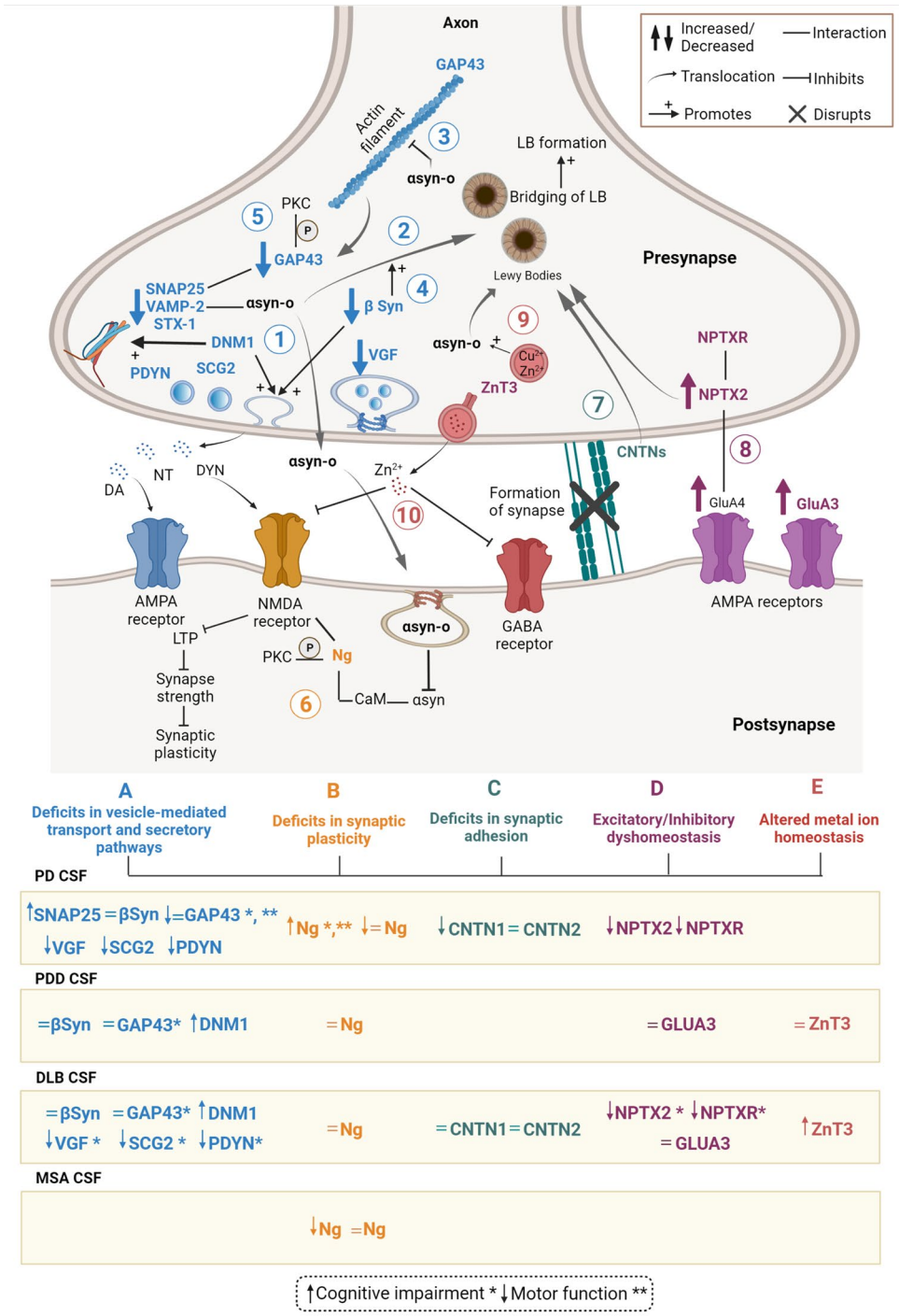

Fig. 1 Schematic representation of mechanisms related to synuclein-mediated synapse degeneration (**A**–**E**) and published findings of related biofluid candidate biomarkers. *LB* lewy body, *DA* dopamine, *βSYN* β-synuclein, *NT* neurotransmitter, *DYN* dynorphins, *CaM* calmodulin. Each mechanism of dysfunction is shown in a different colour, marked **A**–**E**. Explanation of each process can be found in the text. Created with BioRender.com

Studies showing elevated CSF GAP-43 concentrations in Alzheimer's disease patients compared to controls and that CSF GAP-43 concentrations correlated better with Alzheimer pathological burden than with TDP-43 or α-synuclein burden post-mortem suggest the possibility that CSF GAP43 concentrations better reflect Alzheimer-related rather than synuclein-related changes (Remnestal et al. 2016; Sandelius et al. 2019).

Secretory vesicle proteins

A study of CSF DNM1 concentrations in DLB and PDD patients (Fig. 1A, Table 1 Aiii) reported elevated DNM1 compared to subjects with subjective cognitive decline, but concentrations did not correlate with global cognition (Enache et al. 2020). While these results are promising, validation of these findings in independent cohorts is needed.

Secretory granule proteins such as neurosecretory peptide VGF and secretogranin-2 (SCG2) are exclusively expressed in neuronal and neuroendocrine and endocrine cells. A proteomic study of the CSF (Fig. 1A, Table 1 Aiii) revealed that PD and DLB patients as well as patients with other neurodegenerative diseases had significantly lower CSF concentration of VGF and SCG2 compared to controls (van Steenoven et al. 2019, 2020). The finding in DLB was validated in an independent cohort in the same study. Lower CSF concentrations of both proteins were associated with worse global cognitive performance and were lower in DLB compared to all other diseases, including PD (Table 1 Aiii). In summary, preliminary studies suggest that low CSF concentrations of these secretory proteins may be a common feature of neurodegeneration. The potential of these proteins as objective markers of cognitive performance in DLB is promising, but requires follow-up in further independent studies. The potential of secretory proteins as surrogate markers of cognitive decline in synucleinopathies other than DLB and PD also warrants further investigation.

Prodynorphin

One study has reported reduced CSF concentrations of the dense core vesicle protein PDYN in two populations of DLB patients and one population of PD patients compared to healthy controls (Fig. 1A, Table 1 Aiii), albeit that PDYN concentrations were lower in DLB patients compared to PD and other neurodegenerative diseases, suggesting a degree of specificity for DLB, the reason for which is unclear (van Steenoven et al. 2020). They also reported that CSF PDYN concentrations were associated with global cognitive performance in DLB and controls combined (Table 1 Aiii). PDYN is processed at the presynapse to dynorphin opioid peptides in response to potassium-induced depolarization of the neuron (Yakovleva et al. 2006) and is expressed in hypocretin/orexin hypothalamic neurons, which are affected in PD and may be implicated in the sleep disturbances that are a common feature of synucleinopathies (Crocker et al. 2005). Whether this alteration in CSF concentration of PDYN reflects a loss of hypocretin/orexin hypothalamic neurons is an interesting avenue worth pursuing.

Deficits in synaptic plasticity (Fig. 1B)

Another reported mechanism by which α-synuclein oligomers may induce synaptotoxicity is by impairing long-term potentiation (LTP). Specifically, α-synuclein oligomers can reduce *N*-methyl-d-aspartate (NMDA) receptor-mediated synaptic currents producing deficits in visuospatial learning mice (Durante et al. 2019). The kinase activity of protein kinase C (PKC) is necessary for LTP (Abeliovich et al. 1993). Two important substrates of PKC include the presynaptic growth-associated protein-43 (GAP-43) (**5**) and the postsynaptic protein, neurogranin (Ng). In addition to GAP-43 (previously discussed), there is accumulating evidence directly implicating Ng dysfunction in synucleinopathy (**6**). For example, a direct interaction between Ng and α-synuclein has been reported in human brain extracts from the temporal cortex of healthy controls, an interaction that was reduced in PD but not DLB patients, while both PD and DLB patients showed decreased levels of phosphorylated Ng in the temporal cortex compared to controls (Koob et al. 2014).

Neurogranin

Several studies have evaluated CSF Ng as a potential surrogate marker of synapse dysfunction in synucleinopathy-related diseases but with somewhat conflicting results (Fig. 1B, Table 1 B). On one hand, increased CSF Ng concentration has been reported in drug naïve PD patients compared to healthy controls, correlating with both cognitive impairment and motor disease stage (Bereczki et al. 2017). Even more promising, the same study showed that PD patients on dopaminergic therapies showed statistically comparable CSF Ng concentration to controls. On the other hand, another study has reported differences in CSF Ng in the opposite direction; namely, reduced CSF Ng concentration in PD patients compared to controls, correlating with CSF α-synuclein levels, cortical glucose metabolism, and motor stage (Selnes et al. 2017). This was partially supported by another study, which reported lower CSF Ng concentration in patients diagnosed with PD, PDD, and MSA, but not DLB, compared to controls, correlating with markers of tau-mediated and axonal neurodegeneration but not with cognitive dysfunction, motor impairment, or subsequent development of dementia (Hall et al. 2020). Further studies reported no change in CSF Ng concentration between MSA, PD, PDD, or LBD patients and controls (Portelius et al. 2018; Wellington et al. 2016; Janelidze et al. 2016; Remnestal et al. 2016). Thus, the relationship of CSF Ng to clinical diagnosis of synucleinopathy-related diseases is unclear. Studies determining the relationship between CSF Ng and synuclein pathology could shed further light on this matter, but unfortunately are scarce. One study has reported a lack of association between antemortem CSF Ng concentration and post-mortem α-synuclein burden in the amygdala or hippocampus of autopsy-confirmed patients with DLB (Portelius et al. 2018). No data relating to post-mortem α-synuclein burden were available for PD, PDD, or MSA patients.

When interpreting data on CSF Ng, it is important to consider the abundance of studies showing a strong correlation (r values ranging from 0.5 to 0.9) of CSF Ng with

markers of tau-mediated neurodegeneration that is not restricted to Alzheimer's disease and the tauopathies but is also apparent in synucleinopathies such as PD (with and without dementia) and DLB (Portelius et al. 2018; Hall et al. 2020). This raises the possibility that tau comorbidity (likely, Alzheimer-related), which is common in PD, PDD, DLB, and MSA, may be a confounding factor that could explain the conflicting findings for CSF Ng concentrations reported in synucleinopathies. If so, CSF Ng may reflect different processes of synapse degeneration depending on the underlying tau morbidity and could explain the conflicting findings in the literature. Further studies that take into account tau comorbidity in synucleinopathies are needed to fully determine the clinical potential of CSF Ng in synucleinopathy-related diseases. To our knowledge, Ng has yet to be evaluated in plasma or serum from patients with underlying synucleinopathy. However, as plasma Ng concentrations were detectable but unchanged in Alzheimer's disease patients, Ng shows little promise as a blood-based biomarker (De Vos et al. 2015).

Deficits in synapse adhesion (Fig. 1C)

The presence of synapse adhesion molecules, such as the contactins (**7**), in nigral and cortical Lewy bodies in PD patients post-mortem (Chatterjee et al. 2020), suggests that they may play a role in synucleinopathy-mediated degeneration. Synapse adhesion molecules form trans-complexes that span the synaptic cleft (Rudenko 2017) and their expression is regulated by synaptic activity to dynamically scale up or scale down synaptic communication and regulate synaptic plasticity (Fu and Huang 2010; Friedman et al. 2015; Pierre et al. 2001; Tai et al. 2007; Yamada et al. 2007). Contactin-1 (CNTN-1) has a crucial function in regulating synaptic plasticity by promoting neurogenesis in the hippocampus (Puzzo et al. 2013) and cerebellar interneurons (Berglund et al. 1999). Contactin-2 (CNTN-2) regulates axon guidance and synaptogenesis (Stoeckli 2010). Sequestration of synapse adhesion molecules in Lewy bodies (**7**) could therefore affect synapse development and synaptic plasticity, although this has yet to be demonstrated experimentally.

Contactins

Lower CSF CNTN-1 concentrations (Fig. 1A, Table 1 Aii) have been reported in PD patients compared to controls, correlating with CSF α-synuclein and markers of tau-mediated neurodegeneration but not disease stage or duration or global cognitive performance (Chatterjee et al. 2020). The same study showed no statistical difference in CSF CNTN-1 concentration between DLB patients and controls. To explain the apparent specificity of CSF CNTN-1 for PD over DLB, the authors proposed that as contactins are absent or reduced in and around amyloid plaques in Alzheimer's disease brain tissue (Chatterjee et al. 2018), that CNTN-1 sequestration in Lewy bodies may be less prevalent in DLB patients due to more abundant Alzheimer pathology in DLB compared to PD. The idea that CSF CNTN-1 concentrations may be influenced by Alzheimer pathology is supported by the positive correlation between CSF CNTN-1 and CSF markers of tau-mediated neurodegeneration in the DLB patients ($r=0.58$) and controls ($r=0.67$). CSF concentrations of CNTN-2 were nominally elevated but statistically comparable to controls in PD and DLB patients (Chatterjee et al. 2020). In summary, the finding of low CSF CNTN-1 concentrations in PD patients is promising, but the lack of association with cognitive performance or motor scales may limit the utility as a marker of synuclein-mediated synapse degeneration.

Excitatory/inhibitory homeostatic imbalance (Fig. 1D)

α-Synuclein expression in the adult mouse brain is found predominantly at excitatory synapses (Zhang et al. 2019) but is also expressed at inhibitory synapses, particularly in regions most vulnerable to synuclein pathology, such as the olfactory bulb, medulla oblongata, pons, substantia nigra, amygdala, and piriform cortex (Taguchi et al. 2016). In PD patients, both elevated expression of glutamate receptors (NMDA, AMPA, kainite, and metabotropic GluR5) and a loss of GABA-ergic interneurons have been reported (**8**) (Zhang et al. 2019; Khundakar et al. 2016). These findings suggest that over excitation and/or a loss of inhibition are also a feature in synucleinopathy. The importance of regulating excitatory transmission to PD pathogenesis is evident in that anti-PD therapies based on negative allosteric modulation of glutamate receptors improve PD motor symptoms and reduce levodopa-induced dyskinesia (Zhang et al. 2019). Meanwhile, the loss of GABA-ergic interneurons in the visual cortex could explain the recurrent visual hallucinations that are a clinical feature of synucleinopathies (Khundakar et al. 2016). Neuronal pentraxin-2 (NPTX2) is critical to regulating excitatory-inhibitory circuit function (**8**). Specifically, NPTX2 is recruited to the presynapse by the neuronal pentraxin receptor (NPTXR) where increased neural activity stimulates NPTX2 secretion (Lee et al. 2017; Kirkpatrick et al. 2000). NPTX2 then recruits and clusters AMPA receptors at the post-synapse via direct binding to the GluA4 subunit, thus strengthening the excitatory synapse onto GABA-ergic parvalbumin interneurons (Tsui et al. 1996; O'Brien et al. 1999; Xu et al. 2003). Whole-genome expression profiling of the substantia nigra of PD patients and controls revealed NPTX2 as the most highly upregulated gene in PD patients (Moran et al. 2008). Moreover, the same study showed that NPTX2 expression was present

in a subset of Lewy bodies in the substantia nigra and cerebral cortex of PD patients and appeared to form a bridge between Lewy bodies, thus implicating NPTX2 in inclusion growth. Whether NPTX2 expression is also upregulated in DLB and MSA patient brains has yet to be reported. Similar to PDYN, NPTX2 is expressed in hypocretin/orexin hypothalamic nerve cells that are known to be affected in PD and are implicated in the sleep disturbances that are a common feature of synucleinopathies (Crocker et al. 2005). Taken together, disruption of the excitatory/inhibitory homeostatic balance represents another potential mechanism relating pathological α-synuclein to synaptic dysfunction.

Neuronal pentraxins

Studies in CSF (Fig. 1D, Table 1 D) have reported lower CSF NPTX2 and NPTXR concentrations in several cohorts of DLB patients compared to healthy controls, with CSF NPTX2 concentration correlating with global cognitive decline and decline in the visual spatial domain (Boiten et al. 2020; van Steenoven et al. 2020). Although low CSF NPTX2 and NPTXR concentrations were also reported in PD patients, they were significantly lower in DLB compared to PD patients (van Steenoven et al. 2020). In the cognitively normal aged population, low CSF NPTX2 concentrations were associated with less functional connectivity in the salience/ventral attention networks, an association that was stronger among individuals with lower levels of cognitive reserve (Soldan et al. 2019). This may be relevant to DLB where dysfunction in salience and attentional networks have been reported (Sourty et al. 2016; Lowther et al. 2014). The observation that low CSF NPTX2 concentration in DLB patients correlated with low CSF α-synuclein and VGF concentrations (Boiten et al. 2020) is consistent with evidence that NPTX2 expression may be regulated by the VGF/BDNF pathway (Beckmann et al. 2020). Potential mechanisms to explain the low CSF NPTX2 concentrations include a loss of glutamatergic synapses onto GABA-ergic interneurons or, as suggested in post-mortem studies of PD patients, that NPTX2 may accumulate in the brain in Lewy bodies. Taken together, these studies support CSF NPTX2 as a promising biomarker of excitatory/inhibitory homeostatic balance in DLB and PD that requires validation in independent cohorts and is worthy of further investigation in other synucleinopathies. Of particular interest could be further study of the relationship to functional changes in the visuospatial domain in neuroimaging cohorts.

Glutamate receptors

To our knowledge, GluA3 is the only glutamate receptor to be investigated in patient-derived biofluids of the synucleinopathies (Fig. 1D, Table 1 D). CSF concentrations of GluA3 were comparable between PDD and DLB patients and subjects with subjective cognitive impairment (Enache et al. 2020). Studies in other synucleinopathies are lacking.

Altered metal ion homeostasis (Fig. 1E)

Disturbance to metal ion homeostasis represents another potential mechanism involved in α-synuclein-mediated synapse degeneration. α-Synuclein has an exceptionally high binding capacity for Ca^{2+} and an imbalance in calcium or α-synuclein can cause synaptic vesicle clustering in vitro (Lautenschlager et al. 2018). The same study showed that lowering either the levels of α-synuclein or calcium prevented dopamine toxicity. Other metal ions, particularly, Cu^{2+} and Zn^{2+}, induce self-oligomerization of α-synuclein in vitro (Paik et al. 1999) (**9**). Long-term exposure to copper in the workplace is a risk factor for developing PD due to its detrimental effect on dopamine metabolism, oxidative stress, and α-synuclein oligomerization (Bisaglia and Bubacco 2020). Similarly, zinc exposure is an environmental risk factor for PD and zinc deposition has been reported in the substantia nigra and striatum of PD patients post-mortem (Sikora and Ouagazzal 2021). In rodents, elevated zinc causes degeneration of the nigrostriatal dopaminergic pathway and locomotor deficits (Sikora and Ouagazzal 2021). Zinc homeostasis is also critical to synaptic plasticity, which, as discussed above, is impaired by α-synuclein oligomers. The zinc transporter (ZnT3) **(10)**, which is specifically expressed within Zn^{2+}-containing synaptic glutamatergic, GABA-ergic and dopaminergic neurons of the hippocampus, cortex, olfactory bulb, and spinal cord (Ruiz et al. 2004; Wang et al. 2002), is essential for the correct sequestration of Zn^{2+} ions and subsequent release into the synaptic cleft (Lee et al. 2011; Palmiter et al. 1996). The binding of Zn^{2+} ions to the NMDA receptor can potentiate allosteric inhibition of NMDA receptor currents in low extracellular Zn^{2+}concentrations and act as a pore blocker of NMDA receptors at high concentrations (Sensi et al. 2009; Paoletti et al. 1997) **(10)**. There is also evidence that zinc homeostasis may modulate GABA-ergic synaptic transmission **(10)**. ZnT3 knockout mice show diminished $GABA_A$-mediated inhibitory postsynaptic potentials and are resistant to dopamine-induced locomotor deficits and memory impairment (Lopantsev et al. 2003; Sikora and Ouagazzal 2021). Taken together, synaptically released Zn^{2+} from corticostriatal terminals could underlie the motor and cognitive deficits associated with PD and could be related to α-synuclein-mediated effects on synaptic plasticity (Sikora and Ouagazzal 2021).

Ion transporters

A study of CSF concentrations of ZnT3 in DLB and PDD patients (Fig. 1E, Table 1 E) reported significantly elevated ZnT3 concentrations in DLB (and a trend towards elevated ZnT3 in PDD) compared to subjects with subjective cognitive decline (Enache et al. 2020). CSF ZnT3 concentrations did not correlate with global cognition in either DLB or PDD. The utility of CSF ZnT3 as a biomarker of zinc dyshomeostasis in DLB and PDD requires further investigation.

Synaptic proteins as diagnostic fluid biomarkers in syuncleinopathies

Although not a necessary requirement of a surrogate marker of synapse degeneration CSF and blood concentrations of synaptic proteins could potentially aid in the clinical and differential diagnoses of synucleinopathy-related diseases. Table 2 shows the diagnostic accuracies for the synaptic proteins included in this review (either alone or in combination), where reported. In terms of clinical diagnosis (Table 2 a), the highest reported accuracy for a model including synaptic proteins in PD was the oligomeric α-synuclein/VAMP-2 ratio in serum EVs (Agliardi et al. 2021), which gave an area-under-the-curve (AUC) of 0.88 and performed nominally better than serum EV oligomeric α-synuclein alone (AUC = 0.82). CSF biomarkers performed worse than serum EV markers (all AUC < 0.73). A few synaptic proteins have been evaluated in PDD and all showed poor diagnostic accuracy (all AUC < 0.68). In DLB, a combination of CSF Ng, NPTX2, total α-synuclein, and age gave an AUC of 0.94 (Boiten et al. 2020), surpassing any biomarker alone. If validated in other cohorts, this level of accuracy suggests that this model could be used as an additional diagnostic maker for DLB. However, it may be difficult to incorporate into the clinical setting due to the number of analytes needed. We found no studies reporting on diagnostic accuracy of synaptic markers in MSA.

A biomarker that can aid in the differential diagnosis of distinct synucleinopathies and parkinsonian disorders (Table 2b) would also be a welcome addition to the biomarker arsenal. Several studies have tested the performance of various combinations of synaptic biomarkers to distinguish PD from DLB. The best reported model was a combination CNTN-1, total α-synuclein, total tau, phosphorylated tau, and $A\beta_{1\text{-}42}$, which gave an AUC of 0.88 (Chatterjee et al. 2020). Again, the complexity of this combined model may be difficult to implement, but is worthy of further investigation in independent cohorts. The performance of CSF Ng to distinguish PD/PDD and atypical parkinsonian disorders was also reported but performed poorly (AUC = 0.56).

The clinical manifestations of synucleinopathy-related diseases, particularly DLB, can overlap with other neurodegenerative disorders, thus further complicating diagnosis. Thus, a biomarker that can aid the differential diagnosis from other neurodegenerative diseases (Table 2c) would also be useful. Most of the studies included in this review, focused on the differential diagnosis between DLB and AD or DLB/PDD and AD, for which the best reported model was for a combination of VGF, SCG2, and PDYN, with an AUC of 0.89.

In summary, these studies suggest that synaptic proteins, particularly when used in combination with synuclein species, can provide added value as diagnostic biomarkers.

What have we learned from studies of synaptic biomarkers in synucleinopathies?

We have performed a comprehensive review of candidate biomarkers of synapse degeneration in PD, DLB, and MSA patient-derived CSF (14 proteins), serum (1 protein), and serum extracellular vesicles (3 proteins), and placed these findings in the context of the mechanisms associated with α-synuclein-mediated synapse degeneration. We also have discussed their diagnostic accuracy. Based on the findings discussed in this review, we conclude the following:

1. The data provided by neuroimaging tracers provide further evidence that synapse degeneration is a major event in synucleinopathy. Neuroimaging and biofluid markers may provide complementary information as to the cumulative and active effects of a toxic (or therapeutic) agent on the synapse, respectively.
2. Synuclein species may have greater utility as diagnostic or prognostic markers rather than as surrogate markers of synapse degeneration in patients with underlying synucleinopathy.
3. Despite the evidence for synapse degeneration as a driving factor in disease pathogenesis, the synucleinopathies have received relatively less attention than other neurodegenerative diseases. This is particularly true for MSA. For comparison, over 31 candidate CSF synaptic markers have been investigated in over 50 studies of Alzheimer's disease patients to-date. Of all the markers included in this review, only Ng has been evaluated in MSA patient CSF and the results were not replicated across the two studies, so few conclusions can be taken as to the utility of these synaptic markers in MSA patients. This relative lack of attention towards MSA compared to the more common synucleinopathies likely reflects the relative scarcity of MSA cohorts, something

Table 2 Diagnostic accuracy of synaptic proteins in PD, PD dementia, DLB and MSA CSF, and serum EVs

Biomarker model	Biofluid	Test	Ref	AUC	%Se	%Sp	Study
a. Clinical diagnosis							
PD							
αsyn-o/VAMP-2	Serum EV	PD	Controls	0.88*	75	93	(Agliardi et al. 2021)
αsyn-o/STX-1A	Serum EV	PD	Controls	0.87*	86	83	(Agliardi et al. 2021)
αsyn-o	Serum EV	PD	Controls	0.82	78	75	(Agliardi et al. 2021)
VAMP-2	Serum EV	PD	Controls	0.78	81	73	(Agliardi et al. 2021)
STX-1A	Serum EV	PD	Controls	0.75	75	78	(Agliardi et al. 2021)
CNTN-1 + tαsyn + tTau + pTau + $A\beta_{42}$	CSF	PD	Controls	0.73	NR	NR	(Chatterjee et al. 2020)
tα-syn/αsyn-o ratio	Serum EV	PD	Controls	0.71	91	55	(Agliardi et al. 2021)
CNTN-1	CSF	PD	Controls	0.65	NR	NR	(Chatterjee et al. 2020)
CNTN-2	CSF	PD	Controls	0.61	NR	NR	(Chatterjee et al. 2020)
PDD							
Ng	CSF	PD/PDD	Controls	0.68	NR	NR	(Hall et al. 2020)
DNM1	CSF	PDD	SCD	0.68	89	30	(Enache et al. 2020)
ZnT3	CSF	PDD	SCD	0.61	50	86	(Enache et al. 2020)
GluA3	CSF	PDD	SCD	0.58	33	89	(Enache et al. 2020)
DLB							
VGF + NPTX2 + tαsyn + age	CSF	DLB	SCD	0.94*	NR	NR	(Boiten et al. 2020)
VGF + SCG2 + PDYN	CSF	DLB	Controls	0.84	77	85	(van Steenoven et al. 2020)
NPTX2	CSF	DLB	SCD	0.82	NR	NR	(Boiten et al. 2020)
VGF	CSF	DLB	SCD	0.81	NR	NR	(Boiten et al. 2020)
ZnT3	CSF	DLB	SCD	0.75	67	86	(Enache et al. 2020)
tα-syn	CSF	DLB	SCD	0.72	NR	NR	(Boiten et al. 2020)
DNM1	CSF	DLB	SCD	0.70	44	89	(Enache et al. 2020)
GluA3	CSF	DLB	SCD	0.61	48	82	(Enache et al. 2020)
b. Differential diagnosis (synucleinopathies/atypical Parkinsonian disorders)							
CNTN-1 + tαsyn + tTau + pTau + $A\beta_{42}$	CSF	PD	DLB	0.88*	NR	NR	(Chatterjee et al. 2020)
VGF + SCG2 + PDYN	CSF	DLB	PD	0.79	72	80	(van Steenoven et al. 2020)
CNTN-2	CSF	PD	DLB	0.62	NR	NR	(Chatterjee et al. 2020)
Ng	CSF	PD/PDD	Atypical parkinsonian disorders	0.56	NR	NR	(Hall et al. 2020)
c. Differential diagnosis (other neurodegenerative diseases)							
VGF + SCG2 + PDYN	CSF	DLB	AD	0.89*	85	1.00	(van Steenoven et al. 2020)
VGF + NPTX2 + tαsyn + age	CSF	DLB	AD	0.76	NR	NR	(Boiten et al. 2020)
tα-syn	CSF	DLB	AD	0.75	NR	NR	(Boiten et al. 2020)
VGF	CSF	DLB	AD	0.72	NR	NR	(Boiten et al. 2020)
NPTX2	CSF	DLB	AD	0.60	NR	NR	(Boiten et al. 2020)
VGF + SCG2 + PDYN	CSF	DLB	All non-DLB	0.82	69	82	(van Steenoven et al. 2020)
VGF + SCG2 + PDYN	CSF	DLB	Frontotemporal dementia	0.76	73	86	(van Steenoven et al. 2020)
Ng	CSF	PD/PDD	AD	0.84	NR	NR	(Hall et al. 2020)
β-Synuclein	CSF	AD	DLB/PDD	0.80	92	61	(Oeckl et al. 2020)
β-Synuclein	Serum	AD	DLB/PDD	0.74	77	75	(Oeckl et al. 2020)
Ng	CSF	AD	LBD	NR	77	73	(Wellington et al. 2016)
Ng	CSF	AD	PD	NR	77	73	(Wellington et al. 2016)
Ng	CSF	AD	MSA	NR	90	73	(Wellington et al. 2016)

The model tested, biofluid, test group (Test), reference group (Ref), area-under-the-curve (AUC), sensitivity (se), and specificity (sp) are provided as reported in each study for the synaptic proteins included in this review for a. clinical diagnosis, b. differential diagnosis compared to other synucleinopathies or parkinsonian disorders, and c. differential diagnosis compared to other diseases

αsyn-o oligomeric α-synuclein, *tαsyn* total α-synuclein, *tTau* total Tau, *pTau* phosphorylated Tau, *SCD* subjective cognitive decline, *AD* Alzheimer's disease, *LBD* Lewy body dementia. *NR* not reported

AUC > 0.85 are marked*

that will hopefully be addressed as the diagnostic accuracy of MSA improves (Miki et al. 2019). The predominant deposition of α-synuclein in GCI as opposed to Lewy bodies could mean that the mechanisms underlying synapse degeneration in MSA are different to those in PD and DLB thus further highlighting the need for studies in this relatively neglected synucleinopathy.

4. In CSF, the most promising candidate synaptic biomarkers are related to neurotransmitter transport and secretion and excitatory/inhibitory dyshomeostasis. Within the vesicle-mediated transport/secretory pathway, the most promising findings were for VGF, SCG2, and PDYN (which were all reduced in all reported DLB and PD cohorts). CSF concentrations of all three proteins correlated with measures of global cognition. One caveat of this finding is that the analyses were performed in the total dataset, rather than stratified by clinical diagnoses, and as such may merely reflect the stratification of cognitive performance between the healthy controls and the disease groups. As neurotransmitter secretion is common to all synapse populations, these CSF changes likely reflect global synapse loss in affected regions. Data relating to the pentraxins are also promising. Both pentraxins were consistently reduced in multiple DLB cohorts and in one PD cohort and both proteins were associated with cognitive performance. Particularly relevant is the association for NPTX2, which was observed in the DLB patients rather in the pooled dataset and which was specific to the visual domain. NPTX2 forms synapses onto parvalbumin GABA interneurons, a loss of which has been related to visual hallucinations in PD. Whether low CSF NPTX2 in DLB CSF reflects a loss of GABA synapses in the visual cortex is an interesting avenue worth pursuing in neuroimaging cohorts. Although these findings need replication in further independent cohorts, they provide further support to the data implicating dysfunction in the transport and secretion of neurotransmitters and for excitatory/inhibitory dyshomeostasis in synucleinopathies (PD and DLB).
5. Alzheimer comorbidity in synucleinopathies may confound interpretation of some synaptic markers. The reported findings for proteins related to synaptic plasticity (Ng and GAP-43) were inconsistent across studies. Neither protein was altered in DLB CSF compared to controls in any of the 7 cohorts, while in PD and MSA, conflicting results were reported across studies of similar sample size. Nevertheless, elevated CSF concentrations of Ng and SNAP-25 recapitulate findings reported for these biomarkers in Alzheimer's disease CSF and may be explained by the strong correlation of these proteins with CSF markers of tau-mediated neurodegeneration, a hallmark of Alzheimer's disease, and a common feature in synucleinopathies. We found similar inconsistencies in reported findings relating to proteins involved in synapse adhesion (contactins), which also correlated with CSF markers of tau-mediated neurodegeneration. Future studies of Ng, SNAP-25, and CNTN-1 that take underlying Alzheimer's disease comorbidity into account (e.g., using the CSF phosphorylated tau / Aβ42 ratio) could be particularly valuable for minimizing neuropathologic heterogeneity across studies.
6. All biofluid studies discussed here report findings in patients with full-blown disease, when neurodegeneration is likely to have already taken hold. As discussed above, the elevated clearance of neuronal proteins into the CSF due to neuronal degeneration may mask more subtle changes in synaptic proteins attributed to synapse degeneration. The recently published research criteria for prodromal PD (Heinzel et al. 2019) and prodromal DLB (McKeith et al. 2020) may pave the way for future studies in subjects at the prodromal disease stage, which may shed further light on synapse degeneration in earlier disease stages.
7. The only study published to-date reporting free concentrations of a synaptic protein in blood was a study of β-synuclein in serum, which reported negative findings. One study has reported low concentrations of SNARE proteins in serum EVs in PD patients, but the technical limitations of preparing EVs from patient biofluid limit their utility in the clinical setting. Thus, blood-based biomarkers of synapse degeneration in synucleinopathies remain elusive.
8. Combination of synaptic proteins with existing diagnostic biomarkers can give provide good diagnostic accuracy for PD and DLB. More studies comparing CSF synaptic biomarkers across synucleinopathies are needed to fully explore their potential.

In summary, there are several promising candidate biomarkers of synapse dysfunction or degeneration in PD and DLB. The most promising candidates include proteins related to neurotransmitter transport and secretion (ubiquitous across synapses) or to a specific subpopulation of synapses that form excitatory inputs onto GABA-ergic interneurons.

Funding This work was funded by the Fondos de Investigaciones Sanitarias (PI18/00327 to OB) from the "Fondo Europeo de Desarrollo Regional (FEDER)", Unión Europea, "Una manera de hacer Europa" and the "Instituto de Salud Carlos III, Ministerio de Economia y Competitividad, Gobierno de España" (ISCIII) and also by the Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR), Spain & Regional Development Funds, EU Knowledge Industry Valorisation Grants-AGAUR-PRODUCTE (2019 PROD 00088 to OB).

Availability of data and materials Not applicable.

Declarations

Conflict of interest Dr Belbin is inventor of a patent application (EP18382175) pending approval entitled "Markers of synaptopathy in neurodegenerative disease".

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