



# The Role of Synapsins in Neurological Disorders

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**Abstract** Synapsins serve as flagships among the presynaptic proteins due to their abundance on synaptic vesicles and contribution to synaptic communication. Several studies have emphasized the importance of this multi-gene family of neuron-specific phosphoproteins in maintaining brain physiology. In the recent times, increasing evidence has established the relevance of alterations in synapsins as a major determinant in many neurological disorders. Here, we give a comprehensive description of the diverse roles of the synapsin family and the underlying molecular mechanisms that contribute to several neurological disorders. These physiologically important roles of synapsins associated with neurological disorders are just beginning to be understood. A detailed understanding of the diversified expression of synapsins may serve to strategize novel therapeutic approaches for these debilitating neurological disorders.

**Keywords** Synapsin I · Synapsin II · Synapsin III · Neurological disorders

## Introduction

Neuronal transmission has always been considered a crucial subject for research, as all life activities of human beings depend on it. Among the numerous proteins

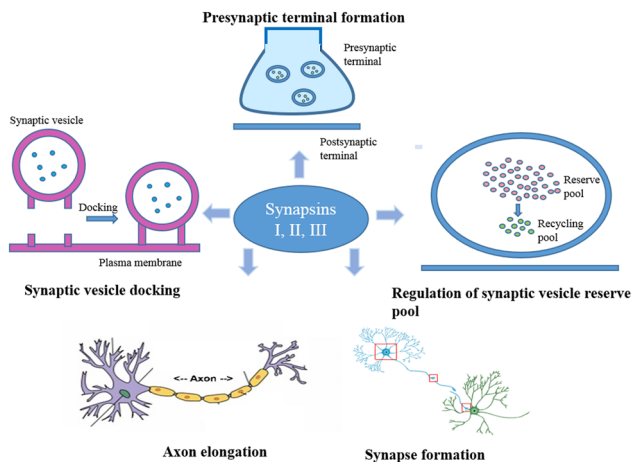
localized within the presynaptic terminals, synapsins serve as the flagships. They were the first presynaptic proteins to be identified and are also the most abundant on synaptic vesicles [1]. As the synapsins are involved in synaptogenesis and neuronal plasticity [2, 3], their alteration may result in neurological disorders like Alzheimer's disease (AD), epilepsy, schizophrenia, multiple sclerosis (MS), and autism spectrum disorder (ASD) [4]. In this review, we systematically discuss the involvement and possible roles of synapsins in various neurological disorders.

## Synapsin Proteins and Subtypes

Synapsins belong to a class of neuron-specific phosphoproteins and comprise ~1% of the total brain proteins, making them one of the most abundant families of synaptic proteins [5]. They have been recognized to be significantly involved in synaptogenesis and neuronal plasticity, including the regulation of synapse development, modulation of neurotransmitter release, and formation of nerve terminals [6–8] (Fig. 1). They act mainly by associating with the synaptic vesicle membrane at the cytoplasmic surface [9]. The binding of synapsins to synaptic vesicles is governed by their phosphorylation state. In the dephosphorylated state, they bind synaptic vesicles, while on phosphorylation they dissociate from the vesicles and mobilize, allowing for eventual exocytosis [10]. In vertebrates, three distinct genes termed Synapsin I, II, and III code for these proteins, while alternative splicing of each of these genes generates distinct isoforms [11–13].

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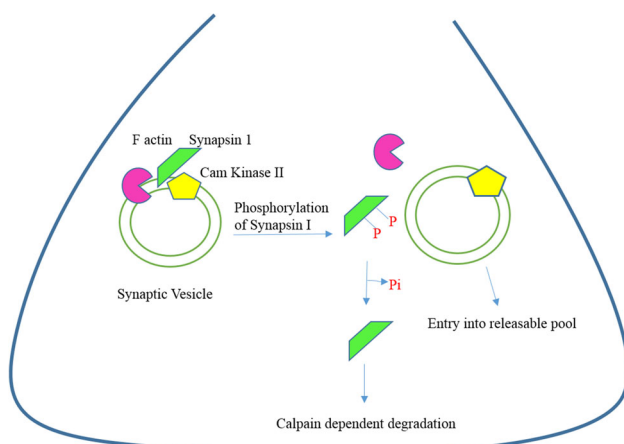
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**Fig. 1** The major functions of synapsins. These neuron-specific phosphoproteins are active in various regulatory functions at the synapses which include the formation of presynaptic terminals, regulation of the vesicle reserve pool at presynaptic terminals, synaptogenesis, elongation of axons, and synaptic vesicle docking.

### Synapsin I

Synapsins are abundant in most nerve cells; however, the different neuronal types have differential distribution of its isoforms [11], with synapsins I and II being the major isoforms in neurons [14]. Synapsin I is associated with elongation of the axon and regulation of the kinetics of synaptic vesicle fusion [15, 16] (Fig. 2). Both isoforms of synapsin I (Ia and Ib) play important roles in synapse formation where they specifically minimize depletion of the neurotransmitter at the inhibitory synapses by contributing to the anchoring of synaptic vesicles [17, 18]. It also regulates synaptogenesis and modulates



**Fig. 2** Synapsin I and synaptic vesicle trafficking. The binding of synapsins to synaptic vesicles is governed by their phosphorylation state. In the dephosphorylated state, they bind synaptic vesicles, while on phosphorylation they dissociate from the vesicles and mobilize, allowing for eventual exocytosis. Phosphorylation of synapsin I plays an important role in mediating the trafficking of synaptic vesicles.

neurotransmitter release as demonstrated by a study on synapsin I-deficient mice. These mice, generated by homologous recombination, revealed altered synaptic vesicle organization at presynaptic terminals in addition to a reduction in neurotransmitter release and delayed recovery of synaptic transmission after neurotransmitter depletion [19].

### Synapsin II

Although synapsin II plays roles in cellular processes similar to those in which synapsin I is involved, many studies have also demonstrated its distinct functions. Knockdown of synapsin II in hippocampal neurons results in deficient axon elongation [20] and disrupted synapse formation [21], indicating its substantial role in synaptogenesis. In addition, synapsin II is considered to be a crucial component of the synaptic vesicle cycle through its involvement in vesicle docking [22]. The synapsin IIa isoform regulates the vesicular reserve pool at glutamatergic synapses [23], while synapsin IIb is involved in the formation of presynaptic terminals [24].

### Synapsin III

Synapsin III is developmentally controlled and predominantly expressed in the early phase of neuronal development; however its role in the regulation of synaptogenesis, neurogenesis, and neuronal plasticity is attributable to active process elongation and changes in axonal differentiation [25, 26]. The regulation of neurotransmitter release by synapsin III proceeds in a manner entirely different from the other isoforms. For instance, knockout (KO) of synapsin III causes a decrease in synaptic depression and an increase in the size of the synaptic vesicle pool, the latter of which is opposite to that in synapsin I- and II-KO animals. Similarly, mice lacking synapsin III do not show abnormal neurotransmitter release at excitatory synapses but only at inhibitory synapses [27]. Moreover, the localization of synapsin III differs, being abundant at extrasynaptic sites and in the growth cones of hippocampal neurons, unlike synapsin I and II which are found mainly at presynaptic nerve terminals [25]. The involvement of synapsins in various cellular processes is summarized in Table 1.

### Association of Synapsins with Neurological Disorders

Synapsin genes have been associated with several neurological disorders such as schizophrenia, bipolar disorder (BD), AD, MS, Huntington's disease (HD), and epilepsy,

**Table 1** Synapsin functions, localization, and associated pathological conditions.

Protein	Accession no.	Functions	Cellular localization	Mutations and SNPs	Associated pathological conditions
Synapsin I	P17600	Chemical synaptic transmission, neurotransmitter secretion, regulation of neurotransmitter secretion and synaptic vesicle exocytosis, synaptic vesicle clustering	Synapse	Q555X [52], A548T [90]	AD, Epilepsy, BD, MS, Huntington's disease, ALS, ASD
Synapsin II	Q92777	Chemical synaptic transmission, neurotransmitter secretion	Synapse, Synaptic vesicle membrane	(rs37733634) A > G [53]	AD, Epilepsy, Schizophrenia, BD, MS, ALS, Hyperalgesia
Synapsin III	O14994	Neurotransmitter secretion, regulation of synaptic transmission	Cell junction, Cytoplasmic vesicle, synaptic vesicle and its membrane	-196G > A [70], -631C > G, -69G > A [73, 81], Ser470N [69]	AD, Schizophrenia, BD, MS

Accession no. and functional categories obtained by UniProtKB.

as demonstrated by both genetic and functional studies. These studies provide satisfactory evidence that a difference in the expression of synapsin genes/proteins is associated with neurological phenotypes and lead to further interest in understanding the potential regulatory mechanisms that underlie these changes.

The present paper systematically reviews the potential derangements in synapsin I, II, and III expression and polymorphisms/mutations that contribute to the pathological consequences associated with various neurological disorders.

## Alzheimer's Disease

AD, the most common form of dementia accounting for more than 80% of the cases reported worldwide [28], is characterized by the progressive loss of cortical neurons that are involved in the mediation of higher cognitive functions [29]. The major clinical manifestations are loss of memory, cognitive dysfunction, and learning deficits [30, 31].

Synaptic loss [32] and neurofibrillary pathology [33] in the limbic system and neocortex are involved in the cognitive alterations in AD patients. Synaptic loss in the dentate gyrus of the hippocampus is predominant in the early phase of development of AD [34]. Regional alterations in synapsin I occur in the hippocampal formation, reported as a significant decrease in the immunoreactivity of synapsin I in the stratum radiatum of the CA1 subfield of the hippocampus and the molecular layer of the dentate gyrus in AD patients [35].

A significant decrease in the level of the synapse-associated proteins glutamate receptor 2, postsynaptic density protein (PSD) 95, and synapsin I after the induction

of endoplasmic reticulum (ER) stress provides further insight into cognitive deficits and defective neurotransmission in the hippocampus in AD [36]. Moreover, a significant loss of the presynaptic markers synapsin-1 and synaptophysin and the postsynaptic markers PSD-95 and synapse-associated protein 97 in individuals with mild cognitive impairment, also indicates the association of posterior cingulate gyrus synaptic function with significant synaptic loss in the prodromal and advanced stages of AD [37, 38].

Interestingly, the sorting-related receptor with A-type repeats (SORLA), which is involved in the inhibition of amyloid precursor protein (APP) trafficking into cellular compartments, also reduces the extent of proteolytic breakdown of APP into neurotoxic amyloid- $\beta$  ( $A\beta$ ) peptide. It interacts strongly with phospho-synapsins I and II and subsequently promotes their degradation by the protease calpain. However, a loss of synapsin-SORLA interaction results in the accumulation of phosphorylated synapsins in the cortex and hippocampus, thereby contributing to synaptic dysfunction in AD [39].

Another interesting notion of the involvement of synapsins in AD was revealed by a study of mutations in presenilin-1 (PS-1), which is one of the major players in AD pathogenesis. Mutations in exon 9 of the PS-1 gene manifest space-occupying "cotton-wool" plaques (CWPs) lacking dense  $A\beta$  cores. The increased synapsin I and synaptophysin immunoreactivity evident in CWPs suggests their potential involvement in synaptic structure and protein expression [40].

Several studies have proposed various treatment strategies targeting the restoration of synaptic proteins levels. In this context Osthole, a natural coumarin derivative isolated from *Cnidium monnieri* (L.), has emerged as a promising therapeutic that exerts its neuroprotective effect by

suppressing the reduction of synaptic proteins synapsin-1, synaptophysin, and PSD 95, resulting in increased micro-RNA-9 expression and a subsequent decrease in  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase kinase 2 and phospho-AMP-activated protein kinase alpha expression [41]. Furthermore, pramlintide, a non-aggregating analog of the hormone amylin, also improves the cognitive defects *via* increased hippocampal synaptic protein expression and can be used as a treatment for AD [42]. A proposed mechanistic approach is presented in Fig. 3, illustrating the potential of osthole and pramlintide.

In accordance with a rise in the number of studies suggesting interactions between synapsins and neurotrophins [43] and APP [44], as well as their association with neuronal plasticity [45], interventions focused on maintaining the expression of synapsins in the brain may be beneficial for populations at a high risk of dementia by delaying the onset of cognitive impairment [46].

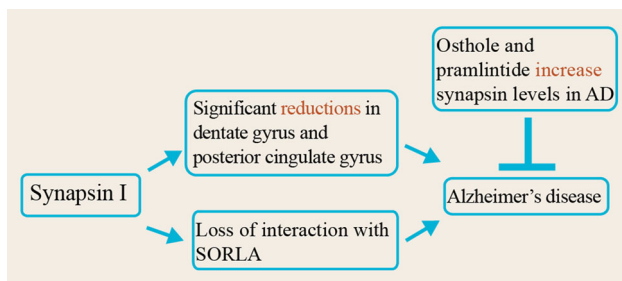
## Epilepsy

Epileptic seizures are one of the most commonly experienced neurological symptoms affecting almost 1% of the world population [46]. It manifests as recurring seizures associated with characteristic signs and/or symptoms of abnormal, excessive, or synchronous neuronal activity caused by persistent cerebral dysfunction [47, 48]. Many studies conducted on synapsin-KO mouse lines have demonstrated that the synapsins play a prominent role in the regulation of neuronal network excitability, and impairment in their function can result in pathological

conditions like epilepsy. The absence of synapsin proteins can elicit epileptic seizures brought about by a range of complex mechanisms, by affecting distinct neuronal populations in various brain areas [49].

A study conducted by Li *et al.* [19] using synapsin I-deficient mice generated by homologous recombination strongly supported the key role of synapsin I in the control of the function of the nerve terminal in mature synapses. In addition, the occurrence of nonsense and missense mutations in synapsin I in epileptic and ASD patients also asserts the notion that the pathogenesis of these diseases is associated with a disturbance of synaptic homeostasis [50]. The first mutation of this kind was reported in 2004 in a four-generation family in which some males expressed an epileptic phenotype either in isolation or in association with mental retardation and/or behavioral disturbances [51]. A more recent study was conducted by Lignani *et al.* in 2015 [52] to understand the involvement of synapsin I mutations in the mechanisms of epileptogenesis through an analysis of the effects of the Q555X mutation on the neurotransmitter release dynamics and short-term plasticity (STP) in excitatory and inhibitory synapses. The results revealed that the network hyperexcitability which leads to the manifestations of epilepsy/autism are triggered by imbalances in STP and the release dynamics of inhibitory and excitatory synapses.

In addition, molecular analysis has suggested that the GABRA6 T > C and Syn II A > G gene polymorphisms are significantly associated with idiopathic generalized epilepsy (IGE) in a south Indian population [53], further suggesting a role for their association with IGE in other ethnicities.



**Fig. 3** Mechanisms of synapsin I involvement in AD pathogenesis and potential treatment strategies aimed at the resumption of synapsin levels. The levels of synapsin I are significantly lower in various brain regions, notably the hippocampus, dentate gyrus, and posterior cingulate gyrus, in AD patients. Furthermore, the sorting-related receptor with A-type repeats (SORLA), which interacts with the phosphosynapsins and causes their degradation, is inhibited in AD. This results in the accumulation of phosphorylated synapsins thereby reducing the levels of unphosphorylated synapsin I. This decrease can potentially be reversed by the use of osthole, a natural coumarin derivative isolated from the leaves of *Cnidium monnieri*, and pramlintide, a non-aggregating analog of the hormone amylin, thus establishing them as promising therapeutic agents against AD.

## Schizophrenia

Schizophrenia is a complex, debilitating neuropsychiatric condition which is believed to be caused by various genetic and neurodevelopmental abnormalities [54]. It is characterized by auditory-verbal hallucinations due to alterations in the information flow between auditory and language processing-related regions [55]. The involvement of synapsins in the pathophysiology of schizophrenia has been determined by different studies which suggest that the pathogenesis of various neurological disorders originate from changes at synapses [56, 57]. Synapsin II and III have been implicated in schizophrenia as a decrease in their expression levels has been found in schizophrenic patients [58–60, 62]; also, single nucleotide polymorphisms (SNPs) have been associated with schizophrenia [62].

The Synapsin II gene, located on chromosome 3p25, has been suggested as a candidate gene for schizophrenia based on functional linkage and association studies. A

significantly reduced protein content of synapsin II [59] has been reported in postmortem studies of schizophrenic brains. Also, there is a substantial decrease in the synapsin II mRNA in the dorsolateral and medial prefrontal cortex of schizophrenic patients, clearly demonstrating its role in the pathophysiology of the disease [60, 61].

The linkage and association of synapsin II gene polymorphisms with schizophrenia have also yielded interesting results. Studies using microsatellite markers and SNPs have revealed a possible involvement of the synapsin II gene in the etiology or pathogenesis of schizophrenia [63]. Using SNPs (rs308963 and rs795009) and two insertion/deletion polymorphisms (rs2307981 and rs2308169) in synapsin II in schizophrenic patients revealed significant differences in the allele frequency distribution between patients and control subjects, further asserting the positive association between synapsin II and schizophrenia [64]. Moreover, a family-based association study has also suggested a role of synapsin II variants in susceptibility to schizophrenia [65].

Synapsin III, located in chromosomal region 22q13 (13.1–13.31), is also considered to be a susceptibility locus for schizophrenia [66, 67]. While a significant reduction in synapsin III protein levels in the prefrontal cortex is recognized as a major cause of dysfunction in schizophrenic patients, molecular studies have identified some polymorphisms in synapsin III which are associated with schizophrenia [68]. The polymorphism S470N in the synapsin III gene affects a phosphorylation site, Ser470, which results in the deletion of a mitogen-activated protein kinase site that is phosphorylated during development and more frequent in probands with schizophrenia than in the normal population. These properties suggest a physiological role for Ser470 polymorphism in neuronal plasticity, which is altered in schizophrenia [69]. The possibility of an association of the SNP-196G/A in the promoter region with schizophrenia has also been reported [70].

However, many studies have negated the idea of involvement of synapsin III polymorphisms in schizophrenia. An association and expression study by Chen *et al.* did not support a major role for synapsin III in susceptibility to schizophrenia in Irish and Chinese populations [71]. Another study by Ohtsuki *et al.* in 2000 involved mutation analysis of the synapsin III gene in schizophrenia using the single-strand conformation polymorphism method. Variants in 13 exons and the 5'-flanking region of the synapsin III gene were searched in schizophrenia which led to the identification of three polymorphisms, y631CrG, y271TrC, and E525Q, and one rare variant, y669C. However, no significant differences in the allelic and genotypic distributions between schizophrenic and control subjects were reported, thus suggesting the absence of an association between the synapsin III gene and schizophrenia [72].

Similarly, three SNPs were identified using a sequencing method, two of which (g.-631C > G and g.-196G > A) were in the 5' promoter regions, while g.69G > A was at exon 1. But no significant differences in genotype or allele frequency distributions of these SNPs were found between patients and non-psychotic individuals, demonstrating no involvement of the synapsin III gene in the pathogenesis of schizophrenia [73]. Moreover, a linkage- and family-based association study also suggested that chromosome 22q13 is not likely to contain a schizophrenia susceptibility gene [74]. Interestingly, studies investigating the DNA methylation and mRNA expression of the synapsin III gene also demonstrated no relation of the variation in SYN III methylation to schizophrenia in the population sample or a monozygotic twin pair discordant for schizophrenia or to the mRNA level of SYN IIIa in different human brain regions [75]. Therefore, despite the evidence of a possible involvement of Synapsin III polymorphisms in schizophrenia, most studies have refuted this idea. On the therapeutic front, there is a positive association of the lifetime use of antipsychotic drugs with synapsin IIa expression in schizophrenic patients, which further implies the involvement of synapsin II in the therapeutic mechanisms of these drugs. This could be further exploited to strategize better therapeutic approaches [61].

## Bipolar Disorder

Pursued as a major topic in health research, BD is a significantly prevalent (1%–2%) psychiatric condition of debilitating nature in the general population. It has been characterized by abnormal episodic shifts in mood ranging from depressive to manic episodes, hindering the carrying out of routine tasks by patients. In BD, the expression of synapsins Ia, IIa, and IIIa is markedly reduced [60].

The involvement of epigenetic regulatory mechanisms in synaptic dysregulation in mood disorders is noteworthy. Interestingly, the synapsin genes are also influenced by these epigenetic factors. Their relationship to enrichment in the H3K4me3 promoter, an epigenetic marker associated with increased transcription, is evident in studies conducted on BD major depression post-mortem brains which show a significant increase in histone modification markers along with a substantial increase in synapsin gene expression [76]. Similarly, a decrease in promoter DNA methylation is also correlated with increased expression of synapsin genes [77].

Moreover, the expression of synapsin is also influenced by alkali metals like lithium. Lithium is a common treatment for BD due to its proven efficacy as a short-term intervention for manic episodes as well as a prophylactic agent against episode recurrence [78].



Abnormalities in synaptic proteins may be a common pathophysiology of BD and schizophrenia, establishing synapsins as a common molecular target for developing better therapeutic strategies for both of these disorders.

## Multiple Sclerosis

Although MS is an autoimmune disease characterized by demyelination in the central nervous system, recent research has revealed that axonal damage characterizes the early stage of the disease. Data based on experimental studies suggest a possible immunogenic role of synapsins, demonstrating an impairment of neurons resulting in the neurological disability of MS [79]. A study by D'Alfonso *et al.* (1999) linked synapsin III to MS as it located the synapsin III gene to chromosome 22q12–q13 which is in close proximity to one of the potential MS susceptibility regions (22q13.1) [80]. In addition, an inverse association of the g.–196 G > A and g.–631C > G polymorphisms at the 5'-promoter region of the synapsin III gene with MS and an association of the g.–631C > G polymorphism with disease onset at a younger age also support the importance of synapsin III as a candidate gene in MS [81].

Also, the significantly decreased expression patterns of synapsin IIa during the early stage of experimental allergic encephalomyelitis strengthen the notion that abnormalities in the release of neurotransmitters and degradation of cytoskeletal elements may contribute to the neuronal deficit [79].

Synapsin-specific T cells, also known as TH1-like T cells [80, 82], have been associated with the pathogenesis of MS, which has been demonstrated to be mediated by TH1-cytokines [83, 84]. Other studies [85] have also reported the presence of synapsin Ia-specific T cells along with a similar frequency of myelin basic protein-specific T cells in the serum of MS patients during different stages of the disease, strongly suggesting a role of synapsins in its development.

## Huntington's Disease

HD is an autosomal dominant neurodegenerative disorder caused by a polyglutamine (polyQ) expansion of >37 glutamines in the HD protein huntingtin (htt) and characterized by motor and cognitive deficits [86]. The degeneration in HD occurs preferentially in striatal neurons and extends to other brain regions with the progression of the disease [87]. The role of synapsins in HD is evident from various research findings suggesting that post-translational modifications in synapsins brought about by HD cause abnormalities. An abnormal phosphorylation state of synapsin I is evident in the striatum and the cerebral cortex of R6/2 transgenic mice expressing an HD mutation. These changes are mostly characterized by early over-phosphorylation at sites 3–5; they have been shown to occur through a decrease in the expression of the calcineurin regulatory subunit-B, contributing to an imbalance between kinase and phosphatase activities. An early impairment in synapsin phosphorylation–dephosphorylation has been marked as a major contributor to changes in synaptic vesicle trafficking and defective neurotransmission in HD [88]. Also, a study on HD CAG150 knock-in mouse brains revealed a strong binding of mutant htt to the C-terminal region of synapsin-1 to reduce its phosphorylation and thus neurotransmitter release, thereby identifying a critical role of synaptic htt in the neurological symptoms of HD [89].

## Others

In addition to their involvement in the conditions discussed above, synapsins have also been linked to conditions like amyotrophic lateral sclerosis (ALS), autism [90], and hyperalgesia [91]. An immunohistochemical investigation of synaptic proteins has revealed differential expression between the two groups of synaptic proteins in the ALS anterior horn of the spinal cord where synaptic vesicle

**Table 2** Mechanisms of synaptic pathology in neurological disorders.

Mechanisms associated with synaptic pathology	Neurological disorders
ER stress-associated neurodegeneration	Synapsin I decrease in AD due to ER stress [36]
Protein Interactions	Synapsin interactions with SORLA in AD [39]
Gene mutations	PS-1 mutation in AD [40], Synapsin I and II mutations in epilepsy [50–53], Synapsin II and III mutations in schizophrenia [63–70]
Altered epigenetic mechanisms	Increased histone modification and decreased promoter DNA methylation in BD [76, 77]
Immunogenicity	Synapsin-specific T cells in MS pathogenesis [82–85]
Post-translational modifications	Impaired phosphorylation in HD [88, 89], Impaired sumoylation in epilepsy and autism [90]

proteins including synapsin I are significantly decreased [92]. In addition, proteomic analysis of the spinal cord in a mouse model of ALS showed under-expression of synapsin II [93]. Although these studies provide a promising association of synapsins, further investigations are required to elaborate its possible involvement in ALS.

ASDs, which are complex, multifactorial neurodevelopmental conditions manifested by impaired behavior and social interaction [94], may also be associated with altered synapsin function. A study by Tang *et al.* in 2015 [90] suggested the possibility of a role of dysfunctional synapsin Ia SUMOylation in neurological disorders like epilepsy and autism. An A548T mutation in synapsin Ia, which is known to be associated with ASD and epilepsy, causes a decrease in synapsin Ia SUMOylation and mirrors the functional defect of non-SUMOylatable synapsin Ia. This study opens avenues for further research on the post-translational modification of synapsins in neurological disorders, creating a paradigm for a better understanding of their role in pathogenesis.

An involvement of synapsin II has also been noted in the synaptic transmission of nociceptive signals in the spinal cord that leads to pain hypersensitivity. A study by Schmidtko *et al.* in 2005 [91] revealed the expression of synapsin II in terminals and neuronal fibers in the superficial laminae of the dorsal horn (laminae I–II). In addition, a unique role of synapsin II in nociception-evoked glutamate release, hyperalgesia, and c-Fos expression in the dorsal horn, assessed through the effects of its complete and transient deficiency on nociceptive behavior in various models, has been attributed partly to its localization as well as function. Although this indicates that synapsins are involved in pain hypersensitivity, further research in this field is imperative for confirmation of this concept. A brief summary is provided in Table 2 listing the involvement of synapsins in neurological disorders.

## Conclusion

The studies conducted on synapsins reveal that each member of the synapsin family has a unique function at a certain type of presynaptic terminal. Alterations in the activity of synapsins may play crucial roles in several neurological disorders. However, our understanding of the possible roles of synapsins in these disorders can be aided by studies aimed at furthering insights into the molecular pathology of the neurological diseases. An understanding of the functions of different synapsins isoforms will also enable us to answer crucial questions about the contributions of synapsins to different brain functions and neurological disorders.

## Compliance with Ethical Standards

**Conflict of interest** The authors report no conflicts of interest.

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