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Review

Do Changes in Synaptic Autophagy Underlie the Cognitive Impairments in Huntington's Disease?

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Abstract. Although Huntington's disease (HD) is classically considered from the perspective of the motor syndrome, the cognitive changes in HD are prominent and often an early manifestation of disease. As such, investigating the underlying pathophysiology of cognitive changes may give insight into important and early neurodegenerative events. In this review, we first discuss evidence from both HD patients and animal models that cognitive changes correlate with early pathological changes at the synapse, an observation that is similarly made in other neurodegenerative conditions that primarily affect cognition. We then describe how autophagy plays a critical role supporting synaptic maintenance in the healthy brain, and how autophagy dysfunction in HD may thereby lead to impaired synaptic maintenance and thus early manifestations of disease.

Keywords: Huntington's disease, cognition, autophagy, synapse, synaptic dysfunction

INTRODUCTION

Huntington's disease (HD) is a progressive neurodegenerative condition characterized by a triad of motor, cognitive, and psychiatric symptoms [1]. Historically, much of the focus on HD has been on the motor symptoms; not only is disease onset defined by their development, but changes in motor symptoms is often the primary outcome measure in therapeutic trials in both preclinical and clinical studies. Notwithstanding, the cognitive impairment and psychiatric symptoms occur earlier, and are often more functionally limiting than the impairments in movement [1–8]. Thus, by studying the molecular mechanisms leading to cognitive dysfunction, we hypothesize that we may be able to gain insight into the early stages of disease pathogenesis.

In this review, we will first explore how cognitive dysfunction is an early manifestation of HD, and that similarly to other neurodegenerative diseases that primarily affect cognition, such as Alzheimer's disease, (AD), dementia with Lewy bodies (DLB), and frontotemporal degeneration (FTD), early deficits in synaptic function may underlie these cognitive symptoms [9, 10]. Next, we will review the growing evidence that the lysosome-mediated degradation pathway autophagy plays a central role in synaptic maintenance, and how the disruption in autophagy may be at the root of the early cognitive changes in HD.

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Table 1
Large cohort studies of HD natural history

Study	Years enrolling	PI	Prodromal vs early clinical HD	Number of participants	Initial reference and website (if available)
PHAROS	1998–2013	Ira Shoulson with the Huntington Study Group	prodromal	1001	[133] Https://huntingtonstudygroup.org/
PREDICT HD	2002–2014	Jane S. Paulsen	prodromal	1078	[22] Https://predict-hd.lab.uiowa.edu/
REGISTRY	2004–2017	G. Bernhard Landwehrmeyer	both	14000	[14]
COHORT	2006–2011	Ira Shoulson with the Huntington Study Group	both	2200	[134]
TRACK	2008–2011	Sarah Tabrizi	both	298	[135]
HD-YAS	2017–2019	Sarah Tabrizi	prodromal	131	[26]
ENROLL HD	2012–present	G. Bernhard Landwehrmeyer	both	still enrolling (20131 as of December, 2020)	[18] Https://enroll-hd.org/

COGNITIVE ALTERATIONS IN HD

> "*the mind becomes more or less impaired, in many amounting to insanity . . . The tendency to insanity . . . is marked.*" *(George Huntington, 1872)*

From the earliest descriptions of HD, such as the well-known manuscript by George Huntington in 1872, the cognitive manifestations of the disease have been recognized [11]. In the broadest terms, these are often in the realm of executive function, such as processing speed and set shifting, although there is a vast literature devoted to better defining the specific cognitive and psychiatric manifestations of disease (for review see [12, 13]). The greatest formal insights into these changes have been gained through the study of prodromal HD patients, defined as patients identified as carrying the expanded CAG repeat mutation, but who have not yet developed the extrapyramidal motor syndrome that defines clinical HD [2]. A series of large observational studies of this patient population have provided clear evidence that cognitive changes in HD occur early and can precede motor symptoms (Table 1) [14–21].

Briefly, neuropsychological testing indicates that prior to being diagnosed with clinical HD, patients demonstrate psychomotor slowing; deficits on tasks requiring sustained attention; and impairments on a range of other executive functions, including set shifting, sequencing, planning, organizing, and cognitive flexibility [15, 17, 22, 23]. There is also data that memory is affected during prodromal HD, but these findings are less clear, as is the subtype of memory that is most affected, such as visual vs. verbal memory or encoding vs. retrieval. These studies also demonstrate that participants with prodromal HD have difficulty recognizing emotions in facial expression and voices, particularly negative emotions such as anger, fear, and disgust, as well as tasks requiring the related concept of "theory of mind," or the ability to consider the world from another person's perspective, as reviewed [2, 24]. These neuropsychiatric features likely begin to develop between 10 and 20 years prior to clinical HD: PREDICT-HD suggested that neurocognitive symptoms could develop up to 15 years before clinical HD [25], whereas the recent HD-Young Adult Study, which evaluated carriers of the expanded CAG repeat who were an average of 23.6 years from predicted clinical HD, found no significant differences in performance on their neuropsychiatric battery relative to control participants, although imaging data suggested that this may in part be due to compensation [26]. Performance on tasks measuring cognitive abilities declines near the onset of clinical HD [27].

SYNAPTIC CHANGES IN HD

It is interesting to note that one of the common themes in neurodegenerative conditions affecting cognition is early synaptic pathology [9]. For example, in AD, synapse loss occurs before cell loss and is a better correlate for cognitive changes than cell loss or the accumulation of pathologic aggregates; and the majority of aggregated alpha-synuclein in post-mortem brains of patients with DLB and Parkinson's disease is found in presynaptic inclusions rather than Lewy bodies in the soma [9]. Indeed, there is a large amount of evidence suggesting that synaptic dysfunction may be an important step in the pathological cascade of HD as well, although as with all autopsy samples, early changes are

difficult to discern. Moreover, correlating findings of neuropathological studies and imaging studies in early disease with the clinical phenotype is often challenging, as subjects are described variably as "prodromal," "presymptomatic," and "premanifest," without a consistent description of the specific assessment scales used to define that clinical stage. Nonetheless, participants labeled with one of these descriptors had not yet begun displaying motor symptoms at a level detectable at the time of last clinical evaluation by the assessments used.

Autopsy studies have long reported neuropathological changes in both pre- and postsynaptic sites in HD post-mortem brain tissue [28–34], but data in subjects with prodromal HD or patients with Vonsattel grades 0 or 1 (suggestive that the samples are analyzed prior to gross cell loss) is limited. Predating Vonsattel grading, medium spiny neurons of adult subjects with clinical HD have been shown to demonstrate morphologic changes in dendrites and alterations in the size, shape, and number of dendritic spines relative to controls [28], which was later confirmed to occur in brains ranging from Vonsattel grades 2–5 [29]. Similar changes were also seen in prefrontal cortical pyramidal cells of Vonsattel grades 2–4 brains from adult HD subjects, in which neurons demonstrated changes to dendritic arborization, length, and surface area [30].

Notably, the finding that the *HD* gene product huntingtin (Htt) aggregates in neuronal intranuclear inclusions and dystrophic neurites on pathology in post-mortem human brain tissue has offered some clarification on when neuronal processes become involved—studies suggest that dystrophic neurites are present in brains of subjects classified as presymptomatic mutant Htt carriers and early HD cases, whereas the appearance of neuronal intranuclear inclusions coincides with motor symptom onset, but may precede cell death [31, 32, 35]. This is consistent with the hypothesis that alterations in axons are an earlier event in pathogenesis. A study that looked directly at HD pathologic samples from participants classified as presymptomatic revealed a decrease in nerve fiber density, and axonal and synaptic markers [33], supporting this hypothesis. In subjects classified as premanifest, decreased density of the astrocytic glutamate transporter GLT-1 has also been reported, suggesting a potential non-neuronal contribution to synaptic dysfunction [36]. These changes as well as a selective decrease in levels of proteins involved in neurotransmitter release have been observed through all subsequent stages of HD (grades 0–4) [34, 36].

Some of the strongest studies suggesting that axonal and synaptic changes are early events in HD are imaging studies, which have demonstrated that many of the early manifestations of HD may be associated with dysfunction in white matter tracts [37, 38]. In patients with early HD, overall cerebral white matter volume is decreased, and that decrease is correlated with impaired performance on cognitive tasks [39]. Studies examining white matter tracts in pre-symptomatic or early HD patients using diffusion tensor imaging demonstrate a decline in tissue integrity, as measured by decreased fractional anisotropy (FA), in multiple cortical regions, the body of the corpus callosum, and the posterior portion of the internal capsule [40, 41]. Rosas et al. found that the change in FA in the body of the corpus callosum correlated with impairments in cognitive function, as measured by the Stroop color word test. A follow up study further corroborated the tract changes in the corpus callosum in pre-manifest and early HD [42]. It is difficult to determine the proximal cause of white matter changes in these studies. Possibilities include synaptic dysfunction leading to a dying back of the axon tracts, deterioration due to cell death, or a primary pathology within the white matter, as might occur as a result of pathological changes within oligodendrocytes. The authors posit that these white matter changes may occur prior to frank neurodegeneration, given that they occur very early in disease, often decades before expected symptom onset; however, the tract changes were not evaluated relative to atrophy in the connected regions, which would have provided further support for that claim. Similar early changes in white matter tracts have been demonstrated in putamen-prefrontal and prefrontal-parietal tracts, but again, these were not evaluated relative to overall atrophy in the connected regions, making it difficult to eliminate the possibility that these findings are secondary to cell loss [43]. In addition, PET imaging studies evaluating radioligand binding to proteins found in striatal synapses such as phosphodiesterase 10A [44] and the D1 and D2 dopamine receptors [45, 46], have shown decreases in patients with HD; however, these studies did not differentiate if this decreased binding was due to focal synapse loss/dysfunction or general cell loss. Another imaging study in HD shed light on the temporal pattern of synapse loss relative to cell death by demonstrating impairments in sensorimotor tracts in participants classified as having pre-manifest HD, and in multiple white matter tracts, including those of the sensorimotor cortex, corpus callosum, prefrontal

cortex, and thalamus in early HD [47]. These affected tracts correlated with deficits in behavioral tasks, but atrophy was only identified in the caudate and corpus callosum, not the thalamus, suggesting that the tract changes to this latter region may predate cell death in the thalamus. Addressing this question from a longitudinal perspective, results of TRACK-HD demonstrated a correlation between the degree of white matter atrophy and progression during the phase of disease prior to onset of motor symptoms, whereas an increase in grey-matter atrophy correlated with impending clinical (i.e., motor) onset [16].

Experimental model systems also strongly support the observation that synaptic dysfunction is an early change in HD. As with human disease, mutant Htt forms neuropil aggregates in mice transgenic for mutant *Htt* [48], and although mouse models of HD can vary significantly in design, nearly every model demonstrates synaptic pathology and synaptic plasticity deficits prior to outright cell loss or motoric changes [49–62]. This has been extensively reviewed previously [63], but it is important to note that these synaptic changes are found even in those models that aim to recapitulate HD genetically. For example, knock in mouse models of HD demonstrate neuropil aggregates [62], axonal degeneration [60], and electrophysiological changes [50]. The electrophysiological changes are not limited to hippocampal circuits but in transgenic models, extend broadly to cortico-thalamic and cortico-striatal projections [53, 56, 57, 64]. Moreover, biochemically, changes in synaptic protein levels have been noted in animal models of HD [65–69], and are associated with a decrease in dopamine release in the striatum, even after controlling for a decrease in overall dopamine content [70]. Work in these animal models suggests that early changes in synaptic signaling may then lead to cell toxicity [71], although cell death is not a common feature in the mouse models. Broadly, the synaptic changes observed in HD are similar to other neurodegenerative diseases of cognition, in that post-mortem samples from patients with AD and DLB show early synaptic pathology, and animal models of AD and of synucleinopathies demonstrate electrophysiological changes and abnormal synapse morphology in relevant brain regions [9].

Although in broad strokes the early cognitive changes coupled with synaptic alterations make HD similar to AD, DLB and FTD, it is important to note that there are also clear distinctions, especially clinically. For example, AD demonstrates early, prominent changes in information encoding due to pathology within the hippocampal circuit [72]. Similarly, although the term FTD includes a heterogeneous group of disorders, this class of degenerative conditions tends to demonstrate executive or language impairments, which correlate anatomically with the pathology seen in the frontal and temporal lobes [73]. These differences likely reflect discrete regional vulnerabilities of the disease-initiating protein, but once initiated, the resultant pathological cascade may be very similar at the molecular level [74].

SYNAPTIC AUTOPHAGY AND COGNITIVE DECLINE

Although early synaptic dysfunction and cognitive decline may be found across neurodegenerative disorders, including HD, what causes this dysfunction remains unclear. Growing evidence suggests that the lysosome-mediated degradation pathway autophagy contributes to maintenance of the synapse (Fig. 1) and, as such, it may be involved in the pathologic cascade leading to synapse dysfunction in neurodegenerative conditions. Given the importance of autophagy in maintaining protein and organellar homeostasis, this might be unsurprising. The specialized pre- and postsynaptic sites are adapted for constant activity, with a high density of proteins that are regularly undergoing assembly and disassembly processes [75]. Studies indicate that many synaptic proteins have regions that are disordered [76], making them vulnerable to changes in protein homeostasis which can drive their irreversible aggregation, and thereby disrupt function. Moreover, pre- and post-synaptic sites are brimming with mitochondria, which are used broadly for ATP production, regulation of reactive oxidative stress, and calcium buffering. Autophagy is the only degradation pathway in the cell that can handle the breadth of cytosolic cargoes at the synapse, with the ability to transport individual proteins to entire organelles to the lysosome [77]. The flexibility of this pathway is achieved by two key facets of this pathway: the autophagosome, a double membrane structure that forms *de novo* to capture cargo; and fusion to the lysosome, an organelle that has the capacity to degrade almost every component of the cell [78].

In model systems, interventions that alter the amount of autophagic activity (both increases and decreases) lead to impairments in learning and memory [79–84], and it is notable that behavioral changes

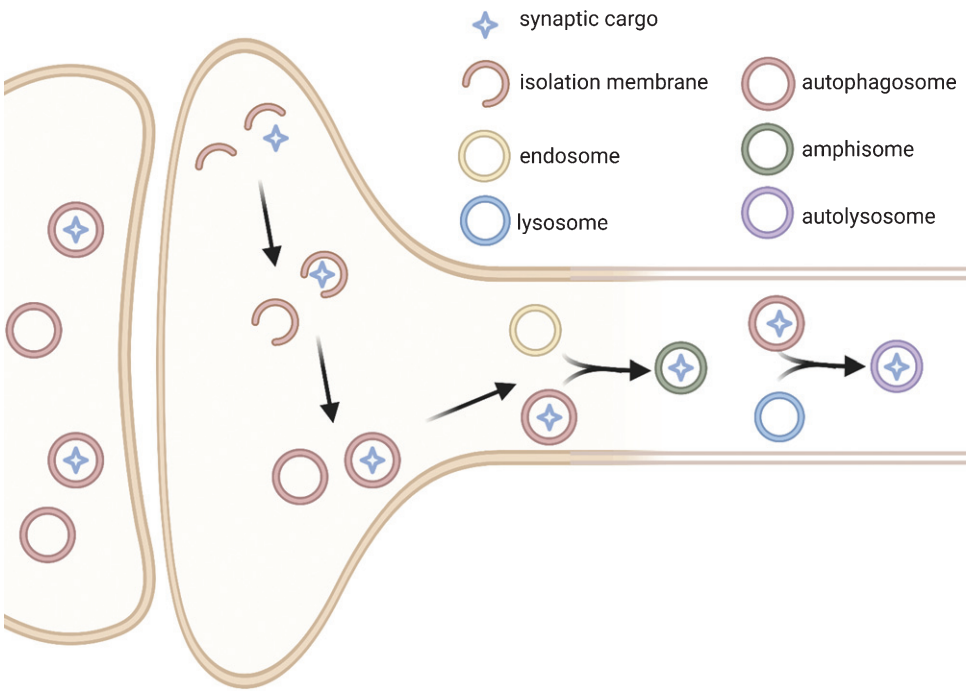

Fig. 1. Simplified schematic of autophagy at the synapse. It has been suggested that pre-synaptically, autophagosome formation is initiated at the synapse by the generation of an isolation membranes that then close to become autophagosomes. These structures then mature as they travel retrogradely up the axon prior to fusing with lysosomes in the cell body [93–100]. The molecular players governing this pathway are still being investigated but may include the proteins Rab-interacting lysosomal protein (RILP) [138] and Endophilin A [94]. Autophagy has been implicated in the processing of various synaptic proteins (see Table 2) and may be involved in the degradation of entire synaptic vesicles [86, 93]. It is unclear how those proteins and organelles are targeted to the autophagosome, but likely requires adaptor proteins such as p62 [106] and Rab26 [93]. The movement of autophagosomes in dendrites has been less thoroughly studied, although autophagy does seem to be playing a role in this compartment as well, as multiple post-synaptic proteins are also implicated as targets of autophagy (see Table 2). (Figure created with BioRender.com).

in response to modulation of autophagy are seen primarily in the cognitive realm. For example, modulation of autophagy in the hippocampus may be important for memory formation, and reversing its decline in aging animals can improve age-related memory deficits [79, 85]. In contrast, disruption of autophagy in dopaminergic neurons does little to disrupt motor performance [86], suggesting that either the reliance on synaptic autophagy is neuronal subtype- or circuit-specific, or that the task itself is less reliant on synaptic flexibility. Interestingly, modulating autophagy in cell culture and animals leads to alterations in dendritic spine morphology and synaptic function [79, 86–92], further supporting the hypothesis that the above changes in learning and memory tasks are mediated by dysregulation of synaptic autophagy.

In animal tissue and neuronal cultures, machinery important for autophagosome formation can be found in the synaptic compartment [93, 94] and autophagosomes that form at the axon terminal mature while travelling retrogradely up the axon to the soma [95–100]. A large number of synaptic proteins have been implicated as targets for autophagy (Table 2) [84, 85, 91, 92, 100–109], suggesting that synaptic proteins are locally taken up by autophagosomes. Many of these proteins are components of the synapse that need to be turned over rapidly in order to facilitate synaptic plasticity, such as proteins required for synaptic vesicle exocytosis, dendritic scaffolding proteins, and post-synaptic neurotransmitter receptors (Table 2). Another feature shared by many of the target proteins is that they have regions that are intrinsically disordered [76], and thus they are aggregation prone, especially if the rate of turnover is decreased. As such, even modest impairments in this function of autophagy could lead to cognitive deficits in tasks that rely on synaptic flexibility.

As further evidence that autophagy plays a specialized role in the healthy synapse, synaptic activity can reciprocally regulate autophagic activity, especially through neuronal electrical activity [90, 94, 101, 105,

Table 2
Synaptic proteins implicated as targets of autophagy

Presynaptic proteins
Ca2 + /calmodulin-dependent protein kinase II (CamK2) [84]
Synaptic Vesicle Glycoprotein 2B (SV2b) [103]
SYD-1 [107]
SYD-2/liprin [107]
Synaptobrevin [103, 107]
Tropomyosin receptor kinase B (TrkB) [108]
Synaptotagmin [100]
Synaptophysin [109]
Postsynaptic proteins
Activity-Regulated Cytoskeleton-Associated Protein (Arc/Arg3.1) [85]
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [104]
glutamate receptor 1 (GluR1) subunit of the AMPA receptor [101, 102]
glutamate receptor 2 (GluR2) subunit of the AMPA receptor [102]
N-Methyl-D-aspartic acid or N-Methyl-D-aspartate receptor 2A (NMDAR2A) [84, 92]
N-Methyl-D-aspartic acid or N-Methyl-D-aspartate receptor 2B (NMDAR2B) [84, 92]
Post-synaptic density protein 95 (PSD-95) [85, 91, 92, 136]
γ-aminobutyric acid A ($GABA_A$) receptor [105]
cholinergic receptor, nicotinic/nicotinic acetylcholine receptor (CHRN) [106]
PTEN-induced kinase 1 (PINK1) [91]
SH3 and multiple ankyrin repeat domains 3 (SHANK3) [91]

Table 3
Synaptic proteins implicated in regulation of autophagy

Snapin [112]
RAB26 [93, 137]
Endophilin A [94]
V100 [113]
Synaptobrevin [114]
Bassoon [103, 115]
Synaptojanin [116]
Brain derived neurotrophic growth factor (BDNF) [91]

107, 110, 111]. Additionally, training on memory-related tasks leads to region-specific increases in markers of autophagic activity, which localize to the brain region necessary for learning of the task [79]. Further, proteins that play a role in synaptic signaling may also regulate autophagy (Table 3) [91, 103, 112–116]. Together, these studies suggest that synaptic signaling fine-tunes autophagic activity as a way to regulate the turnover of proteins in this compartment (Fig. 2).

Despite the accumulation of data supporting the importance of synaptic autophagy in synaptic plasticity, there is still much left to be done in the field. For example, the spatial understanding of where autophagy occurs has been gained largely from embryonic neurons isolated in culture, but has not been confirmed in neurons within adult brains. Moreover, many of the synaptic proteins suggested to be potential autophagic cargo were identified using nonspecific interventions that among other effects, affected levels of autophagic activity, or were simply shown to co-localize with markers of autophagic machinery. Similarly, the studies suggesting a reciprocal relationship between autophagic activity and synaptic signaling did not discern between direct and indirect responses. Although altogether the data is still compelling, the field would benefit from studies using less correlative techniques and, especially in the context of neurodegeneration, studies in the adult and aging brain.

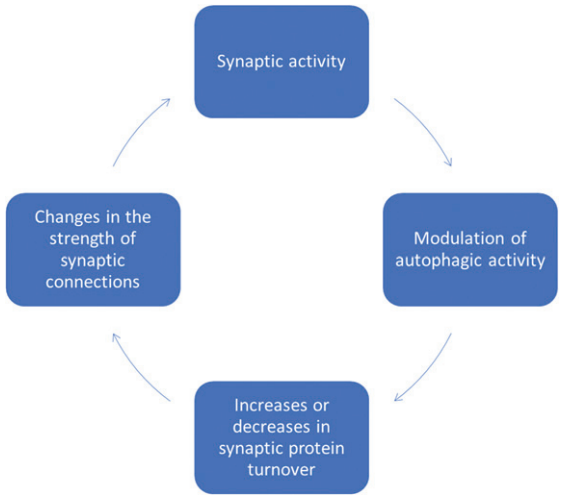

Fig. 2. The interplay between autophagy and synaptic activity. In the normal cell, autophagy is both modulated by [90, 94, 101, 105, 107, 110, 111] and modulates [79, 86, 89, 91] synaptic activity to fine-tune synaptic function. Theoretically, autophagic activity can therefore be up or down regulated to either increase or decrease the amount of synaptic protein turnover. This would modulate the strength of the synaptic connections, and thus the amount of synaptic activity. Synaptic activity can then, in turn, feed back to affect the degree of autophagic activity.

DISRUPTION OF SYNAPTIC MAINTENANCE BY MHTT AND THE ROLE OF AUTOPHAGY

The synapse is an active site that is particularly sensitive to protein homeostasis and membrane trafficking events. Consequently, the mutation underlying HD may be disruptive to the synapse in multiple ways. For example, the expansion of the CAG repeat in the *HD* gene can affect the normal function of the Htt protein, which has been strongly implicating in membrane trafficking. Htt facilitates the transport

of vesicles, including synaptic vesicles, through its interaction with dynein [117], or indirectly with dynactin or with kinesin through Htt-associated protein 1 (HAP1) [118–123]. Further, through interactions with Htt-associated protein 40 (HAP40) [124], Htt also participates in the regulation of endosomal trafficking [125]. As such, the presence of the polyglutamine (polyQ) expansion may interfere with the ability of Htt to interact with its partners, thereby disrupting the trafficking of proteins necessary for synaptic maintenance. Moreover, this disruption in membrane trafficking can also impede autophagy [126] by interfering with the retrograde transport of autophagosomes [127, 128]. Consistent with this, elimination of Htt in Drosophila and the mouse CNS has been reported to decrease autophagic activity [129, 130]. In addition to a direct impact on membrane trafficking, the polyQ expansion can drive aggregation of both the Htt protein as well as its mRNA (reviewed in [127]), placing an increased burden on autophagy as a result of Htt accumulation and thereby impairing autophagic efficiency. Htt may also impact autophagy directly, as it interacts with multiple autophagy related genes, suggesting that it may act as a scaffold for autophagic machinery [129, 130]. Finally, mutant Htt can inhibit Rhes, which through its interaction with mTORC1 can regulate autophagy [131]. Taken together, these data support a model by which mutant Htt leads to decrease in autophagic efficiency, leading to reduced turnover of synaptic proteins and thus cognitive impairment (Fig. 3).

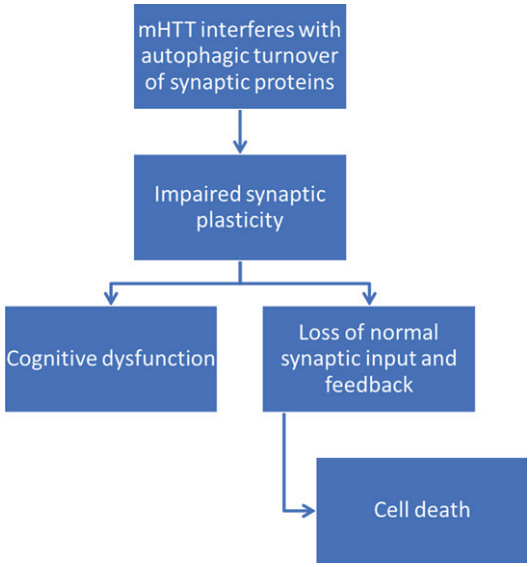

Fig. 3. Proposed pathway of mHtt contribution to cognitive dysfunction and cell death through impairments in synaptic autophagy. mHtt interferes with autophagic efficiency [128–131], leading to a decline in synaptic autophagy. This may in turn interfere with synaptic plasticity, causing both cognitive dysfunction and loss of normal synaptic input to post-synaptic cells and feedback to presynaptic cells. Loss of normal synaptic feedback and input may then contribute to cell death.

CONCLUSIONS

In summary, there is pathologic and imaging data in individuals with mutations in Htt, as well as evidence from animal models with HD, that suggests that synapse dysfunction may occur early in HD, prior to cell death. Autophagy plays a specialized role in the maintenance and function of the synapse, and mHtt may disrupt this function, leading to the early synaptic changes seen in HD patients and model systems. These synaptic changes may then manifest as impairments in synaptic plasticity and thus cognitive changes early in the disease course. Given that neurons rely on synaptic input and feedback for cell health [132], it is possible that this disruption in synaptic signaling in and of itself contributes to cell death in HD (Fig. 3). There is much work yet to be done in this field – although various groups have demonstrated individual components of this pathway, a direct causal relationship of mutant Htt leading to synaptic dysfunction and, in turn, cognitive impairments, has not yet been demonstrated. However, if the model described herein is born out, targeted interventions to improve the efficiency of synaptic autophagy early in the course of HD could be protective against early cognitive changes and potentially degeneration itself.

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