Review

Cognitive Dysfunction in Huntington's Disease: Humans, Mouse Models and Molecular Mechanisms

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Abstract. Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disorder due to an expanded CAG/polyglutamine repeat in the coding region of the huntingtin (htt) gene that causes the preferential degeneration of striatal neurons. Although HD is classically considered a motor disorder, cognitive decline manifests even before the appearance of motor symptoms, and reflects the impairment of additional neuronal populations, such as cortical and hippocampal neurons, in the presence of mutant htt (mhtt). Studies on cognitive dysfunction in HD patients have focused on the cortico-striatal pathway. Here we will describe that HD patients and mouse models share many cognitive defects. Alterations in hippocampal synaptic plasticity and function found in HD mouse models highlight that changes in the functioning of the hippocampal formation contribute to cognitive dysfunction in humans. The similarity between the cognitive dysfunction in HD patients and mouse models has helped to understand better how cognitive dysfunction takes place. Moreover, it validates the use of HD mice to study the molecular mechanisms involved in HD cognitive decline. Several studies in HD mouse models indicate that altered synaptic composition/function, deficient neurotrophic support, kinase/phosphatase imbalance, and transcription dysregulation play an important role in cognitive impairment. This knowledge opens the possibility of identifying relevant therapeutic targets to fight cognitive decline in HD. The finding that in HD many mechanisms are similarly altered in hippocampal and striatal neurons suggests the possibility of a common therapeutic strategy to ameliorate both cognitive and motor dysfunction.

Keywords: BDNF, CBP, hippocampus, LTD, LTP, PKA, striatum

INTRODUCTION

Huntingtin (htt) is expressed in almost all tissues, has a widespread distribution in the brain, its expression levels are similar in control individuals and in Huntington's disease (HD) patients, and there is no evidence of increased htt expression in the brain regions most affected in HD (reviewed by [1]). Thus, several cell-type specific features likely play a role in rendering some neuronal populations more vulnerable to the toxic/malfunctioning effects of mutant htt (mhtt).

A remarkable feature of the brain is synaptic interaction. Given that altered neuronal connections are critical to the appearance of motor deficits, and cortical and striatal neuropathology [2, 3], it is likely that HD pathology firstly occurs in synapses [4] as has been pointed out [5–7]. Cognitive dysfunction

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appears to be the most clear first symptom in HD patients, as well as in mouse models of the disease [8–10]. Cognition is highly related to synaptic function and plasticity, and mhtt is expressed in dendrites and synapses [11, 12]. In fact, mhtt forms aggregates in those subcellular compartments [11]. Moreover, mhtt interacts with several pre- and post-synaptic proteins involved in vesicle transport, receptor internalization, and control of synaptic function [5]. Thus, several questions deserve attention: what is the main role of mhtt in cognitive dysfunction? By which mechanisms can mhtt modify neuronal plasticity leading to cognitive deficits? Is there any molecule or pathway more susceptible to be affected by mhtt, thereby contributing to cognitive decline? Here, we will present studies showing that cortical and striatal malfunctioning, as well as compromised hippocampal function play a role in cognitive impairment in HD patients. Furthermore, we will relate findings in HD humans and mouse models, and we will try to answer those questions by going over the molecular alterations described in HD mice that can underlie, or at least contribute to, cognitive disturbances in humans, as they can be relevant therapeutic targets to fight cognitive decline in HD.

METHODOLOGICAL CONSIDERATIONS

Limitations of human studies

Like other disorders, HD is characterized by a diversity of clinical presentations, rates of progression and responses to therapy, suggesting the existence of different subgroups and possible variations in the underlying pathological processes (reviewed by [13]). The heterogeneity of human patients can account for the discrepancies in the studies showing [14–17] or not [18–20] cognitive deficits in pre-symptomatic HD-gene carriers. In fact, significant differences in cognitive processes between controls and pre-symptomatic HD patients subgroups have been reported [21]. Moreover, it seems that cognitive and neuropsychological pre-clinical alterations in HD do not follow uniformly [17]. Additionally, discrepancies could also depend on the selected tests, and on the low number of subjects used in most of these studies. Regarding neuroimaging techniques, although they have provided essential data to the understanding of HD pathophysiology, there are still some methodological problems to face like individual differences in brain activation due to comorbidity and/or medication, while complex statistical calculations and fallacies in interpreting the results can lead to variability and differences in the conclusions [22–24].

It is also important to mention that some careless interpretations might have been carried out. Cognitive alterations in HD have often been related to cortico-striatal dysfunction, while hippocampal impairment is usually obviated in the interpretation of human HD studies, and can also play an important role in those deficits (see below).

Limitations of studies in HD mouse models

Learning and memory tasks in rodents often involve not only cognitive function but also physical skills. So, in HD mouse models performance in the Morris water maze or acquisition of a motor skill could be influenced by deficiencies not directly related to altered cognition but to fatigue or changes in muscular strength. On the other hand, the generation of HD mouse models using distinct strain backgrounds increases the difficulty of interpreting and compelling findings. In addition, mhtt also differs between mouse models as some express only a portion of the mhtt protein, while others express full-length mhtt, which adds variability mainly in phenotype severity (HD mouse models are reviewed elsewhere; [25, 26]). However, despite these problems and caveats, behavioral tasks studied in rodents have been crucial to reveal many aspects of HD progression, and mouse models have helped to start uncovering the molecular pathways underlying cognitive impairment in HD.

As for human studies, there are some misinterpretations in studies evaluating conditioned motor learning in mice, which although is thought to be mainly mediated by cortico-striatal pathways, can also involve the hippocampus [27]. Similarly, visual discrimination learning, strongly affected in HD mice [28, 29], is usually related to the striatum, but hippocampal function can also be involved in this paradigm [30, 31].

MULTIPLE MEMORY SYSTEMS AND THEIR INTERACTIONS

We will briefly introduce the multiple memory systems since this will be useful to put the reader in context, and because some emerging ideas can help to understand how to integrate findings from studies in humans and in HD mouse models (for complete reviews see [32, 33]).

Classically, the acquisition of new motor skills, the development of instrumental behavior and the formation of habits is thought to involve the striatum. The frontal cortex (together with a cortico-striatal loop) has been implicated in working memory, attention,

and planning of goal-directed behaviors. Finally, several forms of episodic and semantic memories depend on temporal structures like the hippocampus and entorhinal cortex (reviewed by [32–34]). However, it is now generally accepted that there is an interaction between striatal, cortical and hippocampal systems. Thus, the final cognitive outcome can depend on compensatory, competitive or cooperative interactions between systems (reviewed by [35–37]). Importantly, under pathological conditions these interactions become imbalanced, and the performance of one memory system can increase to compensate the functional alterations ongoing in another related system [38]. Given that the limits between memory systems are not so clear [39], cognitive impairment in HD patients can be more difficult to relate to specific neural systems than previously thought.

COGNITIVE DYSFUNCTION IN HD

Several studies in patients and in mouse models of HD have been carried out to identify cognitive deficits and evaluate their progression. Unfortunately, studies in humans have mainly focused on the cortico-striatal function, and less frequently on the hippocampal formation [13] or other brain regions. However, some cognitive tests/abilities involve hippocampal integrity in addition to cortico-striatal function. Evidences from studies in mouse models show that synaptic plasticity alterations are found, not only in striatum, but also in the hippocampus [40], which can explain the hippocampal-related cognitive impairment observed in these animals. In addition, alterations in synaptic plasticity or activity in other brain regions such as the thalamus [41, 42] could also account for cognitive decline observed in HD patients [43]. However, in the present review, we will focus on cortico-striatal and hippocampal synaptic plasticity and function. Table 1 summarizes the cognitive deficits found in HD mouse models that better correlate with those found in patients.

HD patients

In the following sections we will present studies regarding cognitive dysfunction in HD patients in whom impairment of the cortical and striatal function could be playing a main role, and data showing that hippocampal function is also compromised. Cognitive deficits will be classified according to their manifestation: before the onset of motor symptoms (pre-symptomatic individuals), or when motor

Table 1
Summary of the cognitive deficits found in HD mouse models that better correlate with those found in HD patients

Cognitive alterations Pre-symptomatic stage	HD patients References	HD mice Model	References
Lack of strategy-shifting	[50]	R6/1	[28]
		YAC128	[82]
Procedural learning deficits	[57]	R6/1	[258]
		YAC128	[82]
		Knock-in	[94]
Deficiencies in motor learning	[49]	YAC128	[82]
Loss of executive function	[21]	R6/2	[259]
Early-middle stage			
Loss of inhibition in pre-pulse inhibition paradigm	[46]	R6/2 YAC128	[260] [82, 87]
Decreased recognition memory	[67, 261]	R6/1	[88, 90]
		R6/2	[88]
		Knock in	[91, 132]
Spatial learning deficits	[16, 54]	R6/1	[88]
		R6/2	[29]
		Knock-in	[91]

symptoms are already evident (early-middle symptomatic patients). Cortico-striatal-related cognitive alterations seem to appear earlier and be more severe than those likely mediated by the hippocampus and related temporal structures. Thus, mhtt affects differentially distinct brain regions, indicating that there are complex interactions between the mutation and the molecular environment.

Cortico-striatal dysfunction

One of the most common and persistent cognitive deficits in HD patients at pre-symptomatic stages is a difficulty in tasks requiring a shift in strategy [14, 44]. Interestingly, this aberrant response may stem from an inability to inhibit the previously learned response, a process thought to be mediated by the striatum [45]. Reinforcing the idea that loss of inhibition could account for the strategy-shifting deficits observed in humans, it has been demonstrated that there are alterations in the pre-pulse inhibition paradigm in HD patients at early stages [46]. At pre-symptomatic stages, HD patients also show alterations in executive functions, verbal fluency [21, 47], procedural learning, planning, and explicit motor learning [14, 48, 49]. In early-stage symptomatic HD patients, there is also a deficit in discrimination learning and reversal learning, again arguing in favor of perseverance in learned responses [50]. Moreover, attention, acquisition of psychomotor skills, planning, executive functions and memory progressively decline [44, 51–53].

In middle symptomatic HD patients a widespread cognitive decline is observed in which executive

function, verbal fluency, perceptual speed and reasoning are strongly affected [16, 54]. Finally, at more advanced stages, a sub-cortical dementia gradually develops, with alterations in several simple and complex cognitive functions involving slow information processing, decreased motivation, depression, apathy and personality changes [55, 56].

Impairment of the cortico-striatal function in HD patients is also supported by neuroimaging studies. A study using functional magnetic resonance imaging shows alterations in a serial reaction time task paradigm in HD pre-symptomatic individuals with respect to controls. These alterations correlate well with decreased activity in the frontal cortex, and the putamen is also consistently less activated in HD patients than in control individuals [57]. Executive function is impaired in early HD patients correlating with caudate and putamen atrophy [51, 58]. Mild-stage HD patients show less activation of dorso- and ventro-lateral prefrontal cortex, left inferior parietal cortex and left putamen during a parametric verbal working memory task. This reduced activity correlates with a loss of grey matter in these brain regions, and with a lower accuracy in the performance of the task [59]. A reduction in blood flow in caudate, parietal and frontal cortex in middle-stage HD patients, as assessed by high resolution single photon emission computerized tomography, correlates well with poor performance in distinct neuropsychological cognitive tests [60]. Decreased dopamine binding in the striatum of mild to moderate-stage HD patients was also found to correlate with deficits in visuospatial skills, episodic memory, verbal fluency and reasoning [54].

Dysfunction of the hippocampus and temporal structures

To our knowledge, studies focusing on the hippocampal function in HD patients are lacking. However, some of the cognitive tasks used in human studies can involve the participation of the hippocampus and temporal lobe structures. For instance, spatial working memory, spatial recognition memory [61], object recognition memory [62, 63], episodic memories [64, 65], and some forms of associative learning [66] are, at least in part, regulated by the hippocampus.

Pre-symptomatic HD patients show no serious deficits in spatial working memory as they perform well tasks involving these cognitive abilities, although their latency to respond is higher than in controls [14]. On the other hand, pre-symptomatic HD-gene carriers show impairments in recognition memory [67]. In early-mild symptomatic HD patients, there are alterations in associative learning, pattern and spatial short-term memory and in spatial working memory [68]. Although the authors suggested a role for the cortico-striatal circuitry, they did not mention that alterations in the hippocampus and related structures could be also involved. At this stage of the disease, deficits in recall and recognition memory are consistent and clear [69]. In middle-stage HD patients, a rather global cognitive decline is observed including episodic memory and spatial memory deficits [16, 54]. Finally, at more advanced stages, there is a so-called sub-cortical dementia, with alterations in several cognitive functions, some of them likely involving impairment of the hippocampal function [55, 56]. Thus, tasks relying on hippocampal and cortico-temporal integrity (declarative memories: visuospatial, spatial working-memory and object and spatial perception/recognition) are altered in HD patients but to a lesser extent than those dependent on cortico-striatal integrity (procedural learning). This is supported by the finding that, when HD patients have to solve a cognitive task, the hippocampus, which is less impaired, attempts to compensate for striatal dysfunction [70]. It is noteworthy to mention that, according to findings from distinct verbal learning tasks involving the hippocampal function [71], it has been suggested that, in HD, long-term memory is more prone to be affected than short-term memory [13, 16, 72–74].

Interestingly, tests assessing episodic memory and visuomotor abilities significantly correlate with metabolic reductions in temporal cortices [75]. Reductions in dopamine binding have also been correlated with deficits in the Stroop, Digit span and Tower of London tests [76]. Thus, imaging studies also provide evidences that alterations in the temporal region contribute to cognitive defects in HD patients.

HD mouse models

Cortico-striatal impairment

Several cognitive tasks can be used to evaluate cortico-striatal function in rodents as for example delayed-alternation tasks, discrimination tasks, procedural learning tasks and acquisition of new motor skills [77–79]. Performance in delayed-alternation tasks, which are highly dependent on cortico-striatal integrity [78], is strongly affected in HD mouse models at early ages: 5 week-old R6/2 [29], 10 week-old R6/1 [28] and 12 month-old knock-in mice [80]. Furthermore, visual discrimination learning [28, 29], as well as tactile-dependent learning [81], is altered in pre-symptomatic R6 mice. In addition, alterations in strategy-shifting,

a paradigm that can reveal aberrant perseverance on a learned response, are one of the most obvious pre-symptomatic deficits in both exon-1 and full-length HD mouse models [28, 29, 82].

Hippocampal dysfunction

Several tasks involving hippocampal and related temporal structures, such as the Morris water maze [83], spontaneous alternation task [84, 85], and novel object recognition test [86], have been used to evaluate learning and memory in HD mouse models. Spatial learning and navigation are altered at pre-symptomatic stages in R6/1, R6/2, YAC128 and Hdh$^{Q7/Q111}$ mice [29, 87–90]. Moreover, object and spatial recognition memories are also impaired in pre-symptomatic R6/1, R6/2 and Hdh$^{Q7/Q111}$ mice [88, 90, 91]. These impairments persist during disease progression [92, 93]. However, exon-1 mouse models often display a rapid and severe phenotype progression, which does not allow distinguishing the onset of cortico-striatal-related cognitive deficits from those related to the hippocampus. The use of knock-in mice has partially elucidated this question since alterations in cortico-striatal-dependent cognitive tasks, involving delayed alternation and attention, have earlier onset [80, 94, 95] than changes in hippocampal-dependent cognitive tasks such as spatial learning [91]. In agreement with human data, some declarative long-term memories are earlier and more severely altered than short-term memories in both exon-1 and full-length HD mouse models [88, 90, 91, 96]. Furthermore, hippocampus-based learning skills are preserved in R6/2 mice at ages in which striatum-based learning is impaired [97], and hippocampal function can overcome deficits in striatal function [98]. Thereby, compensatory mechanisms operate so that less affected hippocampus balances striatal failure in HD.

SYNAPTIC PLASTICITY ALTERATIONS IN HD MOUSE MODELS

Activity-dependent modifications in synaptic efficacy (synaptic plasticity), such as long-term potentiation (LTP) and long-term depression (LTD), are widely believed to underlie information processing and storage in the brain [99] (for a comprehensive historic overview on LTP and LTD research see [100, 101]). Here, we will present the most relevant findings regarding cortico-striatal and hippocampal plasticity alterations in HD mice. It is intriguing that whereas human studies have focused on

cortico-striatal dysfunction to explain cognitive alterations in HD, researchers using mouse models have mainly focused on hippocampal function and related areas. Accordingly, the hippocampus is the brain region in which almost all synaptic plasticity changes have been described, and whose clear anatomical organization makes its study easy and comfortable. Studies in HD mice have provided several evidences that hippocampal function is strongly affected suggesting that many findings in HD patients could be related to this disturbance. This is relevant because hippocampal, cortical and striatal systems interact to regulate cognitive function.

Cortico-striatal pathway

Electrophysiological studies in cortico-striatal slices from HD mouse models have revealed, in general, earlier and more severe alterations in these connections than in hippocampal synapses [40, 102]. However, the progression of cortico-striatal deficiencies seems to be biphasic. In fact, Ca^{2+} currents in medium-sized spiny neurons (MSNs) are increased in young R6/2 mice, whereas they decrease in symptomatic transgenic mice [103–106]. Interestingly, a propensity towards cortico-striatal synaptic depression is also observed in YAC mice [107]. Studies in different HD mouse models showed that glutamatergic transmission is either increased or decreased respect to wild-type mice [103, 108–110]. In YAC mice, this biphasic effect seems to correlate with an enhanced N-methyl-D-aspartate receptor (NMDAR) response at early ages that then dramatically decreases with age [111], indicating that each phenomenon occurs at different stages of the disease. On the other hand, evoked synaptic responses and spontaneous synaptic currents are both altered in the cortico-striatal pathway, and these alterations get worse as the neurological phenotype advances in HD mice [40].

Some studies have addressed cortical synaptic plasticity in pre-symptomatic HD animals. The study of the representation of the row of vibrissae after associative learning indicates that R6/1 mice display deficits in plasticity in the primary somatosensory cortex [112]. Other studies found deficits in cortical LTP [113–115], which could be rescued by dopamine receptor 1 activation [115]. At relative middle stage of the disease, cortico-striatal LTP is impaired in R6/2 mice [116], a defect that is still present in advanced stages [117]. Furthermore, the inability of cholinergic interneurons to display LTP could facilitate the dysfunction of striatal projecting neurons (reviewed by [118]). At later

symptomatic ages, there is a progressive loss of cell capacitance of MSNs in exon-1 mouse models [103, 109, 119]. This correlates with a loss of cortico-striatal synaptic markers, reduction of dendritic spines, reduced synaptic transmission, and with an inability to express cortico-striatal LTP in the dorsal striatum [116, 117, 119, 120].

Hippocampal pathways

Assessment of hippocampal function has shown that basal neurotransmission at hippocampal synapses (CA3–CA1 field excitatory post-synaptic potentials) appears normal, whereas LTP is reduced in transgenic [28, 121] and knock-in [122, 123] mouse models of HD. A decrease in mossy fiber potentiation was also reported in R6/2 mice [124]. However, at advanced ages, intrinsic membrane properties and action potentials are also altered in R6/1 hippocampal neurons [125], a phenomenon that occurs earlier in striatal neurons [40]. The alteration of the intrinsic electrophysiological properties of hippocampal neurons appears later than LTP and LTD deficits suggesting that neuronal plasticity dysfunction is synaptic in origin. Interestingly, YAC72 mice also show LTP deficits which consist of LTD instead of LTP expression as the disease progresses [126]. Related to this, abnormalities in hippocampal LTD expression seem to be the most conspicuous alteration in different exon-1 HD mouse models [121, 125]. On the other hand, paired pulse facilitation studies indicate that synaptic plasticity deficits observed in full-length [126], as well as in exon-1 [121] mouse models, are mainly due to post-synaptic dysfunction, although a pre-synaptic component should not be ruled out [5]. Considering all these findings, it could be assumed that persistence of synaptic depression is the most conspicuous hippocampal synaptic plasticity alteration, although LTP is also impaired. Moreover, the onset of neuronal plasticity deficits occurs earlier than the development of an overt phenotype, independent of normal synaptic transmission. Finally, a post-synaptic component more than a pre-synaptic component seems to play a main role in those alterations.

MOLECULES AND PATHWAYS IMPLICATED IN COGNITIVE DECLINE IN HD: LESSONS FROM ANIMAL MODELS

Cognition is highly dependent on plasticity processes in which proper synaptic function plays an important role. Thus, in order to design therapeutic

Table 2
Putative molecules contributing to cognitive deficits in HD mice

Protein	Brain region	Mouse model	Type of alteration	References
PSD-95	Striatum	R6/1	Reduced levels	[128]
	Hippocampus		Reduced levels	[90]
GluA1	Hippocampus	R6/1	Reduced levels	[90]
Complexin-II	Striatum Cortex Hippocampus	R6/2	Reduced levels	[149]
Synapsin I	Cortex Striatum	R6/2	Altered phosphorylation levels	[192]
NF-κB	Forebrain	Knock-in	Disrupted synapse-nucleus translocation	[262]
Dopamine receptor 1	Striatum	R6/2	Reduced levels and binding	[138]
Dopamine receptor 2	Striatum	R6/2	Reduced levels and binding	[138]

This table depicts several molecules involved in synaptic plasticity and in learning and memory that have been studied in HD mouse models, but whose alterations have not been directly related to the progression of cognitive decline. The aim is to show potential new therapeutic targets to fight cognitive impairments in HD.

approaches to treat cognitive impairment in HD it is essential to know the molecular alterations that can underlie, or at least contribute to, cognitive disturbances in HD patients. In the next sections we will focus on molecules/pathways involved in synaptic function and plasticity processes that have been shown to be sensitive to the presence of mhtt (Table 2). We will also discuss those that have been demonstrated to be involved in cognitive decline in HD models.

Synaptic molecules

In this section we will go through the changes in synaptic components described in HD that likely contribute to synaptic plasticity defects and cognitive impairment.

At early stages of the disease, when cognitive and plasticity alterations are detected, no changes in the protein levels of any NMDAR subunit are observed in the striatum of HD mouse models [127, 128]. Only a loss of striatal GluN2B subunit has been described in R6/1 mice at late stages of the disease [128]. Conversely, the function of NMDARs is severely altered in HD models [103]. The fact that HD mouse models do not respond to intrastriatal NMDAR agonists [111, 127–130] further supports the idea that intracellular signaling pathways activated by the receptor are affected in HD, which likely contributes to synaptic plasticity impairment and cortico-striatal-dependent cognitive defects.

It is known for almost three decades that NMDARs are essential for the expression of hippocampal LTP [131], and the formation of hippocampal memory [83]. CA3-CA1 LTP deficits in full-length YAC72 and knock-in mice seem to be due, at least in part, to alterations in NMDARs [122, 126], while in R6/2 mice those deficits are NMDAR-independent [121]. Conversely, CA3-CA1 LTD deficits in R6/1 mice are dependent on GluN2B-containing NMDARs [125]. As for the striatum, no alterations in protein levels are observed for any NMDAR subunit in the hippocampus of R6/1 mice at early stages of the disease, when cognitive and plasticity alterations are detected [28], thus suggesting that hippocampal synaptic plasticity dysfunction dependent on NMDARs can be due to changes in downstream signaling.

It is noteworthy that in addition to NMDARs other glutamate receptors could play an important role in hippocampal synaptic dysfunction in HD. A good candidate is the α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor (AMPAR) subunit GluA1 since it is early down-regulated in the hippocampus of HD mouse models [28, 90]. Interestingly, treatment with ampakines, drugs that enhance AMPARs' function, rescues LTP and object recognition memory in a knock-in mouse model of HD [132]. On the other hand, dopamine receptors, which are able to modulate synaptic plasticity in cortico-striatal and hippocampal connections (reviewed by [133]), are profoundly altered in the caudate-putamen of HD patients [76, 134–137], and in the striatum of mouse models [138–140] from very early stages of the disease. Actually, dopamine deficits can also contribute to LTD deficiencies reported in the perirhinal cortex [113], and to LTP defects found in the dorsal striatum [116], and in the prefrontal cortex [115] of HD transgenic mice.

In addition to receptors, alterations in scaffolding proteins are suitable to contribute to synaptic dysfunction in HD. To our knowledge, the most studied is post-synaptic density-95 (PSD-95). PSD-95 is a post-synaptic scaffold protein that stabilizes NMDARs and AMPARs [141, 142] and modulates their function [143]. Moreover, PSD-95 anchors calcium/calmodulin-dependent protein kinase II (CaMKII), SynGAP and neuronal nitric oxide synthase [144, 145], and thus it is crucial for signaling downstream NMDARs. In HD mouse models PSD-95 is reduced in the striatum and hippocampus from very early stages [90, 127, 128]. Importantly, PSD-95 directly interacts with htt and polyglutamine expansions increase this interaction removing it from the synapse and altering neurotransmission [146]. On the other hand, loss of complexin-II, a protein that regulates fusion processes between synaptic vesicles and the plasma membrane [147], has been shown in PC12 cells expressing mhtt [148], in several brain regions of R6/2 mice, including the cortex, striatum and hippocampus [149], and in the striatum [150] and frontal cortex [151] of HD patients. Interestingly, and supporting a role for complexin-II reduction in HD cognitive impairment, complexin-II knockout mice display learning deficits [152], and impairment of LTP in the CA3 region of the hippocampus [124] similar to those observed in R6/2 mice.

Another emerging player in synaptic alterations is protein kinase C and casein kinase substrate in neurons protein 1 (PACSIN1). PACSIN1 is a neurospecific phosphoprotein with a central role in synaptic vesicle and receptor recycling [153]. Aberrant interaction with mhtt removes PACSIN1 from the synapses in the cortex of pre-symptomatic and early-stage HD patients [151, 154], which likely limits its function in the stabilization of synaptic proteins and receptors. Given the dramatic changes in PACSIN1 found in HD patients, it would be relevant to study in mouse models whether they might contribute to synaptic plasticity alterations, and cognitive impairment.

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, has emerged as an important regulator of synaptic plasticity, and several cognitive processes (reviewed by [155]). Interestingly, whereas htt positively regulates BDNF expression, mhtt impairs BDNF transcription and transport along axons and dendrites [156–160]. BDNF is highly expressed in the regions with highest dysfunction rates in HD (cortex, striatum and hippocampus), and striatal cells are highly dependent on BDNF for survival and function [161–163]. BDNF down-regulation is a widespread phenomenon in HD brain, observed in patients and in mouse models of the disease [28, 122, 164–166]. On the other hand, the BDNF high-affinity receptor TrkB is also reduced in HD models [167, 168], so the complete BDNF-TrkB system is strongly affected in HD. Given that BDNF/TrkB signaling enhances LTP induction not only in hippocampal neurons [169], but also in MSNs [170], their down-regulation is expected to contribute to striatal [116, 171], as well as hippocampal [122, 123] LTP impairment described in HD models. Therefore, deficient BDNF signaling likely plays an important role in synaptic dysfunction, and learning and memory defects

in HD. Actually, BDNF levels regulate the onset and severity of cognitive and motor symptoms, and synaptic plasticity deficits in HD mouse models [28, 122, 172]. Moreover, it has been shown that decreased activity-dependent BDNF expression contributes to cortical microcircuit hypo-connectivity in HD cells [173]. Interestingly, treatments focused on the recovery of BDNF levels successfully improve synaptic plasticity, and motor and cognitive functions in HD mouse models [117, 132, 165, 174].

By which mechanism can BDNF deficits alter synaptic plasticity and cognitive function? The BDNF-TrkB system activates three main signaling pathways: the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway, the phosphatidylinositol 3-kinase (PI3K)-Akt pathway, and the phospholipase Cγ (PLCγ) pathway (reviewed by [175]). ERK1/2 and Akt pathways are not altered in the hippocampus of R6/1 animals at early ages [88, 176, 177], when cognitive symptoms are already observed [28, 88]. Conversely, PLCγ activity is strongly reduced in the hippocampus of young R6/1 mice [28]. These findings are relevant because the main effect of BDNF on LTP expression is basically modulated by the PLCγ pathway [178, 179], and hippocampal LTP is impaired in HD mice.

Kinase-phosphatase imbalance

Memory formation and synaptic plasticity processes rely on balanced kinase and phosphatase activities [180–182]. Several phosphatases are altered in HD mouse models [183] and, most importantly, in the caudate/putamen of HD patients [135, 176, 184]. Strikingly, to our knowledge, their expression levels in post-mortem cortical and hippocampal samples from HD patients have not been analyzed. As many phosphatases altered in HD play a role in memory and plasticity, this imbalance likely contributes to synaptic alterations and cognitive impairment in HD.

Calcineurin plays an important role in synaptic plasticity, and learning and memory [185–189]. Interestingly, it is enriched in MSNs [190], and thus variations in its expression levels/activity can seriously alter their function. Calcineurin levels are reduced in R6 mice striatum [140, 184, 191, 192], and lower calcineurin activity has been shown in the striatum of YAC128 mice at 12 months of age [193]. Conversely, in R6/1 mice hippocampal calcineurin activity is unchanged from 4 to 30 weeks of age [88], and calcineurin levels are unaltered in the cortex [184]. Cortical calcineurin protein levels are also unaffected

in Hdh$^{Q111/Q111}$ and Hdh$^{Q111/Q7}$ mice, but its activity is significantly higher than in Hdh$^{Q7/Q7}$ mice [194]. Thus, it is expected that alterations in calcineurin activity contribute to striatal, and possibly cortical, synaptic dysfunction in HD, while the hippocampus is likely not affected by changes in calcineurin levels/activity.

PHLPP (Pleckstrin homology (PH) domain leucine-rich repeat protein phosphatase)1α is reduced in the striatum of exon-1 and full-length HD mouse models [176]. Additionally, PHLPP1α levels are also decreased in the cortex and hippocampus of R6/1 mice. Since PHLPP negatively regulates the Ras–Raf–MEK–ERK pathway [195], and participates in learning and memory [196], it is likely that those alterations in PHLPP levels can contribute to cognitive defects in HD, but this issue remains to be addressed.

STEP (striatal-enriched protein tyrosine phosphatase) plays an important role in synaptic plasticity through the opposition to synaptic strengthening, and alterations in STEP activity contribute to aberrant synaptic function and to cognitive impairment in several neuropsychiatric disorders [197]. We recently reported that R6/1 mice display reduced STEP protein levels in the striatum and cortex, and increased phosphorylation levels (increased inactivity) in the striatum, cortex and hippocampus [177]. Given that STEP is enriched in MSNs [198], and expressed at lower levels in the cortex, hippocampus and amygdala [199], aberrant STEP levels/activity, are likely to play a role in cognitive impairment in HD. Reduced STEP activity in HD can lead directly, or via the kinase Fyn, to increased activity of the NMDAR subunit 2B [200], which can possibly produce LTD [201]. Interestingly, R6 mice show an aberrant facilitation of LTD expression in the hippocampus by 3–4 months of age [125]. Despite all the evidences supporting a putative role for STEP in cognitive dysfunction in HD, this hypothesis remains to be tested.

Regardless of several supportive evidences, a role for the alterations of distinct phosphatases in the cognitive decline observed in HD remains to be directly demonstrated. In contrast, we recently showed that cognitive dysfunction in R6 mice correlates with increased hippocampal cAMP-regulated protein kinase (PKA) activity, as indicated by the hyper-phosphorylation of several PKA substrates localized at the membrane [88]. PKA plays an important role in the expression of hippocampal-dependent memories [202]. In agreement, inhibition of hippocampal PKA hyper-activity reestablishes long-term recognition memory in R6 mice indicating that

PKA-dependent processes are occluded in HD mice hippocampus [88]. Interestingly, we also reported a dysregulation of the PKA pathway in the striatum of R6/1 mice [177]. Of note, cAMP immunoreactivity is increased in the striatum of R6 mice [203, 204], and PKA substrates as GluN1 and STEP are hyper-phosphorylated in the striatum of exon-1 and/or full-length mouse models of HD at pre-symptomatic stages [128, 177]. Given the cognitive deficits found in striatal-dependent learning tasks in R6 mice [28, 29], it is tempting to speculate that aberrant PKA signaling can also contribute to this impairment.

Another kinase playing an important role in synaptic plasticity, and learning and memory is CaMKII [182, 205, 206]. To our knowledge, hippocampal CaMKII levels have not been analyzed in HD mouse models, but reduced levels have been found in the striatum [207] and cortex [208] of R6/2 mice at 6 weeks of age, and in the synaptic plasma membrane fraction of R6/1 striatum at 12 weeks of age [128]. Thus, these changes could contribute to synaptic plasticity alterations, and learning and memory defects in HD, but this issue needs to be directly addressed.

Summing up, alterations in kinase and phosphatase activities in HD are likely to contribute, directly or indirectly, to changes in relevant signaling pathways involved synaptic plasticity and activity-dependent gene transcription underlying learning and memory processes. Thus, kinases and phosphatases might be interesting therapeutic targets to investigate in the context of HD cognitive decline.

Transcriptional dysfunction and cognitive impairment

Consistent with mhtt interaction with several transcription factors, transcriptional dysregulation is a well-documented phenomenon in HD [209, 210]. Given that learning and memory depend not only on activity-dependent synaptic plasticity, but also on changes in neuronal gene expression [211, 212], it is likely that alterations in transcription pathways/machinery contribute to cognitive deficits in HD. cAMP-responsive element binding protein (CREB) plays a critical role in hippocampal-dependent synaptic plasticity and long-term memory [202, 213, 214]. Despite the aforementioned hyper-activity of PKA signaling [88], the phosphorylation levels of CREB, a nuclear PKA substrate, are not increased in the hippocampus of R6 mice [88]. Similarly, no changes in CREB phosphorylation levels were found in the hippocampus of Hdh$^{Q7/Q111}$ knock-in mice [91]. The

transcriptional activity of CREB not only depends on CREB phosphorylation, but also on the recruitment of specific co-activators [215, 216]. In contrast to the unaltered phosphorylation levels of CREB, the expression of the CREB co-activator CREB-binding protein (CBP), and of CREB/CBP target genes related to memory, such c-fos, Arc and Nr4a2, is reduced in the hippocampus of Hdh$^{Q7/Q111}$ mice [91]. Loss of CBP has also been shown in the striatum of HD mouse models, and improvement of CBP function is neuroprotective [217, 218]. Regarding to cognitive functions, mice heterozygous for CBP exhibit synaptic plasticity and memory deficits, as well as impaired rotarod performance [219], and mice with a mutation in the CREB-binding domain of CBP also have motor learning deficits [220]. These alterations are quite similar to those observed in HD mouse models. Besides being a CREB co-activator, CBP possesses histone acetyltransferase activity [221], which alters chromatin structure allowing gene transcription. Interestingly, treatment with a histone deacetylase inhibitor improves motor impairment in R6/2 mice [222], and memory deficits in Hdh$^{Q7/Q111}$ mice [91]. Given that altered CBP levels/function is a common feature in different HD brain regions, CBP could be a good therapeutic target for general cognitive improvement.

THE TRIPARTITE SYNAPSE: A ROLE FOR ASTROCYTES IN HD COGNITIVE DECLINE?

The idea that astrocytes could play an important role in plasticity and cognitive processes has been increasing [223–226]. Moreover, neuroimaging studies showing the precise coordination between the activities of neurons and astrocytes [227] suggest that findings from studies in humans might reveal neuronal as well as astrocytic dysfunction in HD.

In HD individuals, mhtt is also present in astrocytes [228], and expression of mhtt exclusively in astrocytes causes disease, although the progression is slower [229–231]. Moreover, the number of dendrites is reduced leading to neuronal atrophy [232]. With the "tripartite synapse" concept in mind [223–225], the aforementioned studies also suggest that mhtt expression in astrocytes could play a role in the alteration of synaptic plasticity in HD. Moreover, since cerebral blood flow is regulated by astrocytes (reviewed by [233]), the finding that pre-symptomatic HD patients already present resting decreased cerebral blood flow in the prefrontal cortex and putamen [234, 235] could indicate that there are early alterations in astrocytes in

HD. Nevertheless, the precise role of astrocytes in cognitive decline in HD still warrants further investigation.

THERAPEUTIC APPROACHES TO COGNITIVE IMPROVEMENT

Nowadays, available therapies for HD include symptomatic treatments to improve motor dysfunction and depression, while treatments for cognitive symptoms have not yet been developed. So far, based on the assumption that an impairment of cholinergic pathways is also involved in cognitive dysfunction in HD (for review see [236, 237]), treatments used to ameliorate cognitive decline in HD patients are those used with the same purpose in other neurodegenerative disorders such as Alzheimer's disease. However, no improvements have been observed in HD patients treated with acetylcholinesterase inhibitors like donepezil [238, 239] and rivastagmine [240–242]. Conversely, a short-term administration of latrepirdine, a weak acetylcholinesterase inhibitor, has been shown to be well tolerated in HD patients, and to provide some beneficial effects on cognition, but further investigations are needed to prove its therapeutic efficacy [243].

Beside these therapeutic approaches, no other clinical trials have been designed to analyze whether drugs targeting molecular pathways involved in learning and memory [244] could be used to fight cognitive decline in HD. Therefore, there is a need to develop alternative strategies, and we have to take advantage from data obtained by analyzing HD mouse models. New therapeutic strategies can be developed based on altered molecular mechanisms leading to cognitive dysfunction (Fig. 1), and on pharmacological treatments showing benefits in mouse models. As discussed before, the BDNF trophic pathway is down-regulated in neurons affected in HD, and consequently treatments focused on the recovery of BDNF levels improve both motor and cognitive deficits in several mouse models of the disease [117, 122, 165, 166, 172]. In addition, pharmacological treatments with molecules such as cystamine and cysteamine [245], CEP-1347 [246], sertraline [247, 248], ampakine [132, 174], rolipram [249] or TP-10 [250] have been shown to improve HD phenotype in mouse models, possibly by increasing endogenous BDNF levels. Interestingly, there are non-pharmacological approaches that improve BDNF levels, and that have already been shown to be beneficial in HD mouse models. Environmental enrichment induces beneficial effects in HD mouse models (reviewed by [251]) in part through increased expression of endogenous BDNF [252, 253]. Likewise,

dietary restriction slows the progression of neuropathological, behavioral, and metabolic alterations, and increases BDNF levels in the striatum and cortex of HD mice [254]. Accumulated evidence indicates that sirtuins (Sirt), NAD-dependent protein deacetylases, are involved in the beneficial effects of caloric restriction [255]. Recently, Sirt1 was shown to prevent mhtt-induced decline in BDNF levels [256], and BDNF was identified as a key target of Sirt1 transcriptional activity. While mhtt interferes with CREB-regulated transcriptional coactivator (CRTC) 1 (also known as transducer of regulated CREB activity, TORC1)-CREB interaction to repress BDNF transcription, Sirt1 rescues this defect both *in vitro* and *in vivo* [257]. Thus, Sirt1 can be an additional therapeutic target to improve BDNF levels and cognitive function in HD.

Additional evidences of possible treatments to enhance cognition in HD come from studies showing alterations in hippocampal PKA activity in R6 animals [88], and in histone acetylation in knock-in mice [91]. We have recently shown that PKA over-activation in the hippocampus contributes to long-term memory deficits in R6 mice [88]. In agreement, we observed that intra-hippocampal administration of a PKA inhibitor reestablishes long-term recognition memory [88]. Moreover, PKA over-activation is also observed in striatal cells expressing exon-1 mhtt [177], thus suggesting that inhibition of the PKA pathway could be also a good therapy to ameliorate motor symptoms. Decreased histone acetylation in the hippocampus has been shown to contribute to memory dysfunction in a knock-in mouse model of HD, and treatment with the HDAC inhibitor TSA reverses long-term memory impairments [91]. Interestingly, administration of HDAC inhibitors to HD mouse models has been shown to improve survival and motor performance in the rotarod, and to normalize striatal atrophy and prevent brain weight loss (reviewed by [217]). Thus, targeting PKA hyper-activity and histone hypo-acetylation in HD could serve to ameliorate cortico-striatal and hippocampal-dependent cognitive function, as well as motor symptoms.

CONCLUSIONS AND FUTURE DIRECTIONS

The study of the molecular mechanisms underlying cognitive dysfunction in HD mouse models demonstrates that many of the molecular pathways affected by mhtt are common to different types of neurons. Conversely, the real contribution of astrocytes to synaptic
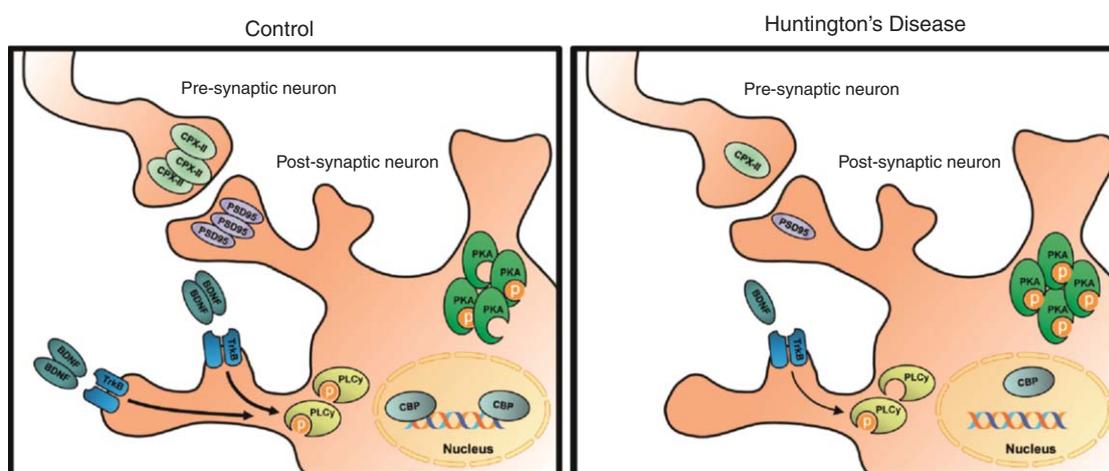
Fig. 1. Diagram showing putative therapeutic targets to improve cognitive decline in HD. Striatal- and hippocampal-related cognitive deficits in HD could be caused by alterations in different pathways. Control and HD conditions are depicted for comparisons. 1, Down-regulation of complexin-II could account for decreased pre-synaptic activity and function. 2, PSD-95 down-regulation and sequestration by mhtt could induce an aberrant downstream signaling mediated by glutamate synaptic receptors. 3, Aberrant PKA hyper-phosphorylation and activity would lead to a phenomenon of synaptic occlusion. 4, A dramatic decrease in the BDNF-TrkB system affects downstream signaling important for synaptic plasticity and memory via the PLCy pathway. 5, Decreased CBP levels prompt to transcriptional dysregulation and histone hypo-acetylation levels. Abbreviations: BDNF, brain-derived neurotrophic factor; CBP, CREB-binding protein; CPX-II, complexin-II; PKA, cAMP-regulated protein kinase; PLCy, phospholipase C-gamma; PSD-95, post-synaptic density-95; TrkB: tropomyosin receptor kinase B.

plasticity alterations, and to cognitive impairment in HD remains to be investigated. This knowledge will lead to therapeutic advances, as the possibility arises that the same treatment might improve both cognitive and motor symptoms. In this way, our future challenge is to design novel tools to treat cognitive symptoms in HD based on these findings. As cognitive deficits detected in mouse models resemble those observed in HD patients, this encourages the search of novel therapeutic approaches, as treatments that improve phenotype in mouse models should be also effective in the human pathology. In addition, it will also be important to test whether a pharmacological treatment is equally efficient when started either before or after cognitive and motor symptoms have appeared. Moreover, we consider that pharmacological treatments designed to improve only motor or cognitive symptoms should be revised in order to determine whether they are good therapeutic strategies to counteract both symptoms. Finally, as some of these treatments, in addition to ameliorate symptoms, are also neuroprotective it should be expected that they would stop or help to slow down the progression of the disease.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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