Cognitive Dysfunction in Huntington's Disease:

Mechanisms and Therapeutic Strategies Beyond BDNF

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Abstract

One of the main focuses in Huntington's disease (HD) research, as well as in most of the neurodegenerative diseases, is the development of new therapeutic strategies, as currently there is no treatment to delay or prevent the progression of the disease. Neuronal dysfunction and neuronal death in HD are caused by a combination of interrelated pathogenic processes that lead to motor, cognitive and psychiatric symptoms. Understanding how mutant huntingtin impacts on a plethora of cellular functions could help to identify new molecular targets. Although HD has been classically classified as a neurodegenerative disease affecting voluntary movement, lately cognitive dysfunction is receiving increased attention as it is very invalidating for patients. Thus, an ambitious goal in HD research is to find altered molecular mechanisms that contribute to cognitive decline. In this review we have focused on those findings related to corticostriatal and hippocampal cognitive dysfunction in HD, as well as on the underlying molecular mechanisms, which constitute potential therapeutic targets. These include alterations in synaptic plasticity, transcriptional machinery, and neurotrophic and neurotransmitter signaling.

INTRODUCTION

In Huntington's disease (HD), the trinucleotide (CAG) repeat expansion in the *huntingtin* gene results in an extended polyglutamine (polyQ) tract in the huntingtin protein which induces a cascade of pathological changes leading to neuronal dysfunction and neurodegeneration. HD is characterized by degeneration of the striatum and cortical atrophy (1,2), but other brain areas such as the hippocampus, thalamus, globus pallidus, and *substantia nigra* are also affected (2-9). Importantly, evidence from both patients (10) and mouse models (11,12) indicates that cell death does not occur until late stages of the disease, indicating that neuronal dysfunction, including abnormal synaptic plasticity, is an early pathogenic event that precedes neuronal death and leads to HD symptoms. Having this in mind, research is focused on finding common molecular targets to prevent cognitive impairment by preserving/restoring neuronal function at early disease stages, which hopefully will help to avoid subsequent neuronal death. Thus, the identification of these early cellular and molecular pathogenic events in HD represents an important milestone in the design of new therapeutic approaches to cure or delay disease progression. To achieve this goal it is mandatory to build from data obtained by analyzing HD mouse models, as new therapeutic strategies can be developed based on those altered molecular mechanisms found to contribute to cognitive impairment in HD.

Cognitive dysfunction in HD patients

The first paper on cognitive function in HD was published in 1974 (13), and relevant publications on this issue have emerged at an accelerating rate since then (reviewed in (14)), so that the nature and variety of cognitive decline in HD patients are well documented and have been the focus of recent reviews (15-19).

Corticostriatal dysfunction

Although HD is characterized by a progressive degeneration of medium-sized striatal spiny neurons (MSNs) (20,21), functional and morphological changes in the neocortex have been proposed as the initial triggers of striatal pathology, and it has been put forward that cortical changes are fundamental for the onset and progression of the HD

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phenotype, in both humans and animal models (reviewed in (22)). In this context, HD patients at pre-symptomatic stages exhibit alterations in tasks related to the neocortical function, like those that require strategy shift (23,24), and also in executive function, in verbal fluency (25,26), in procedural learning, in planning, and in explicit motor learning (25,27-29). Moreover, early corticostriatal alterations in HD patients have been further attested by neuroimaging studies showing impaired corticostriatal functional connectivity in pre-symptomatic HD subjects (30-32). These corticostriatal alterations correlate with decreased activity in the frontal cortex and putamen (33). In mid-stage clinically symptomatic HD patients, executive function, verbal fluency, perceptual speed and reasoning are strongly affected (34,35), while at more advanced disease 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 (36,37).

Marked nuclear and cytoplasmic accumulation of mutant huntingtin has been reported in cortical pyramidal neurons, which overlaps with cortical dendritic abnormalities in postmortem brain of patients with low-grade striatal pathology (38,39). Indeed, abundant mutant huntingtin is evident in numerous cortical dystrophic axons that project to the striatum (40). It has also been reported that stage I and II HD patients exhibit specific thinning of the neocortex (5,41). Overall, these findings indicate that cortical changes are fundamental to the onset and progression of the HD phenotype, evidencing a central role of the cortex at early stages of HD.

Hippocampal dysfunction

The hippocampus, together with the amygdala and the nucleus accumbens, forms the central axis of the limbic system that plays a key role in the formation of declarative memory, spatial learning and awareness, navigation, object recognition and visual memory, as well as in executive functions (42-49). Studies in HD patients have mainly focused on the cognitive functions involving the corticostriatal circuitry, whereas those related to hippocampal connectivity are still poorly analyzed. Nevertheless, there is clear evidence of hippocampal morphological alterations in HD patients such as a reduction in hippocampal volume (4,8,9) and the presence of mutant huntingtin aggregates (3,6). Moreover, some cognitive tasks analyzed in human studies such as

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the evaluation of spatial working memory, spatial recognition memory, object recognition memory, episodic memories and some forms of associative learning, can involve the participation of the hippocampus and temporal lobe structures (43,45,48,50-52). Thus, although no severe deficits in spatial working memory have been shown in pre-symptomatic HD patients, their latency in performing these tasks is higher than in control individuals (24,27), whereas recognition memory has been shown to be affected in pre-symptomatic HD-gene carriers (53). A recent study using tests analogous to those employed in HD mouse models describes hippocampal-dependent impairments in patients in early HD stage, ahead of motor symptoms. Patients are unable to learn the location of the platform in the virtual Morris water maze and performance correlates to the estimated years to disease onset (54). In early-mild symptomatic HD patients, alterations in associative learning, spatial short-term memory, spatial working memory and recognition memory have been described (55,56). Importantly, in middle and more advanced disease stages, a global cognitive decline is observed in HD patients (34-37). These alterations involve both corticostriatal and hippocampal dysfunction. However, it seems that declarative memories more related to hippocampal and corticotemporal functions are not as altered as procedural learning, more related to corticostriatal integrity. Actually, in HD patients, the hippocampus compensates for gradual dysfunction of the caudate nucleus, helping to maintain route recognition close to normal performance (57,58).

Impaired synaptic plasticity and cognitive dysfunction in HD mouse models

The discovery of the gene mutation responsible for HD occurred in 1993 (59), and this allowed for the generation of several HD genetic models. Although the disease has been reproduced in diverse species, mouse models are the most extensively used. The different genetic mouse models differ in their phenotypes as a result of the way mutant huntingtin is inserted into the murine genome: 1) exon-1 transgenic mice: R6, N171-82Q and the conditional HD94Q-tet off mice, and 2) full-length transgenic mice: Yeast artificial chromosome (YAC), bacteria artificial chromosome (BAC)HD and knock-in mice (Table 1). HD mouse models display alterations in synaptic plasticity (Table 2) and replicate the cognitive impairment observed in HD patients (Table 3), thus

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providing an excellent opportunity to study the underlying molecular mechanisms and to test potential treatments for transfer to patients (for review see (60-63)).

Electrophysiology is one of the best characterized methods to evaluate synaptic plasticity. Long-term potentiation (LTP) and long-term depression (LTD) are commonly used paradigms to assess synaptic properties (42,64-66). Several studies indicate that excitatory synapses exhibit the most important alterations in HD (67-69), and numerous reports have concluded that corticostriatal and hippocampal synaptic plasticity are impaired (Table 2). These studies suggest that synaptic deficits, including alterations in synaptic transmission, plasticity and aberrant spine density/morphology, may be the initial triggers of the cognitive deficits observed in HD (70). Interestingly, a recent study using a corticostriatal co-culture cell model from wild-type and YAC128 mice demonstrated impaired development of excitatory synaptic connectivity and reduced dendritic complexity in YAC128 MSNs. Moreover, a number of other HD-associated synaptopathy features previously reported in the striatum of HD mice at mid-to-late stages (71) were also observed (72). Remarkably, mutant huntingtin is required pre- and post-synaptically to elicit these effects, which is in agreement with previous findings showing that its expression selectively in either striatal or cortical neurons is insufficient to fully recapitulate HD behavioral and neuropathological phenotype (73-75). In the same line, the absence of mutant huntingtin in cortical afferents partially improves striatal neuronal activity and behavior in a conditional mouse model of HD (76). Altogether, these studies point to the existence of cell-cell pathogenic interactions that shape the progression of striatal deficits.

Altered mechanisms underlying synaptic dysfunction and cognitive impairment in HD

Neuronal dysfunction and cognitive impairment precede motor symptoms and neuronal death in HD patients, and they occur long before (or in the absence) of cell death in HD mouse models, suggesting that the early cognitive deficits may be a consequence of synaptic dysfunction rather than of cell loss (126,155-158). In fact, huntingtin binds to a wide range of intracellular proteins, many of them responsible for synaptic transmission (159), and mutant huntingtin is present in pre-synaptic (160,161) and post-synaptic terminals (162), where it interacts with several synapse-

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related proteins impairing synaptic function in HD mice (161,163,164). Moreover, the presence of mutant huntingtin alters numerous cellular and molecular mechanisms including protein aggregation, protein-protein interaction, calcium signaling, mitochondrial function, transcriptional regulation and chromatin remodeling, vesicle transport, neurotransmitter release and receptor activity (163-165). Potentially, all these alterations can impact on neuronal functioning, synaptic plasticity and, ultimately, cognitive function. Nevertheless, in the following sections we will mainly focus on those altered mechanisms that have been demonstrated to participate in neuronal dysfunction leading to synaptic plasticity deficits and/or cognitive impairment.

Spine loss

Dendritic spines play critical roles in synaptic transmission and plasticity because changes in their morphology and density modulate the formation and maintenance of the synapses, enabling the dynamics of neural circuitry (166-168). Several studies demonstrate synaptic alterations in MSNs neurons (20,169) and in prefrontal cortical pyramidal neurons (170) from HD post-mortem brain samples. Furthermore, studies in HD mouse models also provide evidence for altered dendritic morphology (Table 2). Here, we describe the mechanisms that contribute to these alterations.

RhoGEF/GAP signaling: Kalirin-7

Kalirin-7, a postsynaptic brain-specific guanine exchange factor protein for Rho-like small GTPases (171), has emerged as a key regulator of excitatory synapses. Overexpression of Kalirin-7 causes an increase in dendritic spine density, spine size and synapse number, while Kalirin-7 knockdown promotes spine shrinkage and loss in cultured hippocampal and cortical neurons (172-175). Importantly, and consistent with *in vitro* experiments, these alterations in excitatory synapses correlate with a decline in the magnitude of the hippocampal LTP and reduced glutamatergic synaptic transmission in the cortex, and impaired cognitive function (173-177), thus supporting a role for Kalirin-7 in learning and memory processes through the modulation of structural plasticity. Interestingly, Kalirin interacts with huntingtin-associated protein 1 (178), and alterations in excitatory synapses occur at early disease stages in HD animal

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models (67,68,134). These synaptic alterations have been suggested as contributing to cognitive symptoms in both HD patients and animal models (56,120,147,149). In a recent study, and following a broad analysis of synaptic-related proteins such as NMDA (GluN1 and GluN2B) and AMPA (GluA1) receptor subunits, presynaptic (VGlut1 and synaptophysin) and postsynaptic (Kalirin-7, PSD95, Shank3 and CaMKII) scaffolding and signaling proteins, only Kalirin-7 showed an early and specific reduction in the cortex of Hdh$^{Q7/Q111}$ and R6/1 mice, which correlates with cortical dendritic spine alteration, impaired corticostriatal synaptic plasticity and motor and procedural learning behavioral deficits in 2- and 6-month-old Hdh$^{Q7/Q111}$ mice (136). Supporting the hypothesis that loss of Kalirin-7 in the cortex of young HD mice could be associated with the early loss of excitatory synapses in HD, Kalirin-7 overexpression restores the number of cortical glutamatergic synapses in mature cultured HD cortical neurons (136).

GluN3A

NMDARs play crucial roles in remodeling and maintaining excitatory synapses, and their activity is altered in MSNs from HD mice (179). NMDAR hyper-function can be detected in HD MSNs at early stages (180,181), well before synapse and spine loss, behavioral deficits and neuronal death, pointing to signaling through these receptors as a key player in the HD pathogenic cascade.

PACSIN1 controls the endocytic removal of GluN3A-containing NMDARs (182). GluN3A is highly expressed in the brain during early postnatal development to prevent premature synapse plasticity and stabilization, but its expression declines afterwards (130,183-185). Nevertheless, a recent study found that mutant huntingtin binds to and sequesters PACSIN1, causing its subcellular redistribution away from the synapse and promoting accumulation of GluN3A-containing NMDARs at the surface of striatal neurons. In agreement, GluN3A levels are increased in human HD striatum and in striatal membrane fractions obtained from distinct HD mouse models including R6/1, YAC128 and Hdh^{Q111} knock-in mice (130), suggesting that this redistribution of GluN3A has a pathological role. The contribution of GluN3A reactivation in MSNs as an important factor in HD pathogenesis receives support from the finding that overexpression of GluN3A replicates the reduced synaptic connectivity observed in

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MSNs from YAC128 mice, whereas lack of GluN3A corrects the early enhancement of NMDAR currents and prevents both early and progressive dendritic spine pathology in MSNs from YAC128 mice. Importantly, it also ameliorates striatum-dependent motor and cognitive decline (130). Thus, these studies reveal a novel early disease mechanism that mediates NMDAR dysfunction and synapse loss in HD MSNs.

Store-operated Ca^{2+} entry

GluN3A deletion experiments suggest that GluN3A expression is necessary to/permissive of HD pathogenesis (130). Nevertheless, other parallel mechanisms seem to be set in motion by the presence of mutant huntingtin, leading to spine loss in HD MSNs. Dysregulation of intracellular neuronal Ca^{2+} signaling plays a role in HD progression (186-188). Mutant huntingtin interacts with type 1 inositol-1,4,5-trisphosphate receptor (InsP3R1), a neuronal endoplasmic reticulum (ER) Ca^{2+} release channel, causing its overactivation and excessive Ca^{2+} release from the ER (189,190). Ca^{2+} release from the ER stimulates neuronal store-operated Ca^{2+} entry (nSOC) channels in the plasma membrane (191), and this pathway plays an important role in the maintenance of postsynaptic mushroom spines in hippocampal neurons (192-194). Interestingly, elevated nSOC was reported in cultured MSNs from YAC128 mice (195), suggesting that aberrant InsP3R1 function and disrupted ER Ca^{2+} homeostasis could contribute to spine loss in MSNs in HD. Interestingly, InsP3R1 knockdown suppresses Ca^{2+} leak from the ER, reduces nSOC levels in spines and is sufficient to prevent spine loss in YAC128 MSNs (131).

Impaired neurotrophic signaling: TrkB/p75[NTR] imbalance

A deficit in neurotrophic support is considered a key player in HD neuropathology. In particular, a reduction in BDNF protein levels was reported in several brain regions of HD patients and mouse models (165,196-200). However, this general finding has not been replicated in a recent study where cortical BDNF mRNA levels were assessed in BACHD and heterozygous Q175 knock-in mice using multiple primers and reference genes (201), thus challenging the view that this neurotrophic deficit is a major pathogenic mechanism in HD.

BDNF exerts trophic effects by binding to its receptors TrkB and p75^{NTR}. BDNF binding to TrkB receptor has been shown to promote neuronal survival (202,203), while BDNF binding to p75^{NTR} could either potentiate Trk function (204-207) or activate cell death cascades (208-210). Notably, whereas BDNF induces hippocampal LTP through TrkB (211), p75^{NTR} has been involved in regulating LTD without affecting LTP (212,213) (for review see (214)). These alterations in synaptic transmission are associated with structural changes. Thus, a deficiency in BDNF-mediated intracellular signaling causes dendritic abnormalities in the striatum and cerebral cortex (215,216), while activation of p75^{NTR} blocks axonal and dendritic elongation and arborization by activation of RhoA, a Rho GTPase that negatively regulates neurite elongation and actin assembly (213,217).

Importantly, reduced TrkB levels have been reported in HD cellular and mouse models, as well as in HD patients (218-220). Moreover, there is increased p75^{NTR} mRNA expression in the caudate, but not in the cortex, of HD patients (220). Therefore, there is an imbalance between TrkB and p75^{NTR} expression in the caudate nucleus of HD patients, and in the striatum and hippocampus, but not in the cortex, of HD mouse models at early stages of the disease (135,221), suggesting that this imbalance contributes to early and progressive HD pathology. Interestingly, genetic normalization of p75^{NTR} in Hdh$^{Q7/Q111}$ mice rescues hippocampal synaptic plasticity and memory function, and prevents hippocampal dendritic spine alterations, likely by normalization of RhoA GTPase activity (107,135). Reinforcing the role of p75^{NTR} in cognitive deficits in HD, overexpression of p75^{NTR} in the hippocampus of wild-type animals reproduces those memory deficits observed in HD mice (135,135), while specific hippocampal p75^{NTR} knockdown prevents the manifestation of cognitive impairment. Together, these findings demonstrate that p75^{NTR} upregulation plays a role in the synaptic and learning and memory deficits observed in HD mice. In agreement with these data, overexpression of p75^{NTR} in hippocampal neurons decreases spine density (222), while null p75^{NTR} mice exhibit increased hippocampal dendritic spine density, improved spatial learning and enhanced LTP (223,224). In addition, Plotkin and colleagues have shown that although cortical production of BDNF, its delivery to the striatum and activation of TrkB are normal in BACHD and heterozygous knock-in zQ175 HD mice, BDNF fails to support corticostriatal LTP specifically at corticostriatal synapses of the

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indirect pathway. Importantly, this kind of plasticity can be rescued by knocking down p75[NTR] or inhibiting its downstream targets RhoA, ROCK and phosphatase and tensin homolog deleted on chromosome 10 (PTEN), indicating that enhanced signaling through p75[NTR] and PTEN antagonizes TrkB function and corticostriatal LTP (201). It remains to be determined whether this improvement in corticostriatal connectivity can be reproduced in other HD models, and whether it translates into an amelioration of corticostriatal-dependent learning and/or motor symptoms.

Cognitive impairment

Adenosine type 2A receptor

HD mouse models display reduced reversal learning and working memory deficits (102,120,147-149,154,225-229) like early HD patients (230,231). This type of cognitive impairment, which significantly affects the patient's quality of life, represents a primary dysfunction of the corticostriatal pathway (67,232). In a recent study, Chen and colleagues (233) evaluated the ability of adenosine type 2A receptor (A2AR) inactivation to reverse the deficits in working memory and synaptic plasticity at early stages of HD. Their results show that genetic or pharmacological inactivation of A2AR prevents working memory deficits in R6/2 mice, without modifying motor dysfunction. Moreover, although wild-type and R6/2 mice display similar LTD and LTP at corticostriatal synapses, and pharmacological blockade of A2AR inhibits LTP to a similar extent in both genotypes, it selectively reduces LTD amplitude in mutant mice (233). Thus, striatal A2AR emerges as a novel target to fight against the cognitive inflexibility, namely working memory impairment, reported in the prodromal phase of HD (18,231).

PKA overactivation

Synaptic plasticity and learning and memory processes depend on an appropriate balance between kinase and phosphatase activities (234-236). Changes in the expression and activity of different phosphatases (237-246) and kinases (139,242,243,247-253) (and reviewed in (254)) have been reported in HD models and human brain, suggesting that aberrant function of these proteins likely contributes to HD pathogenesis. Although alterations in distinct phosphatases can potentially contribute, directly or indirectly, to synaptic plasticity deficits and cognitive decline in

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HD, this issue remains to be directly addressed (230). Conversely, it has been demonstrated that adenosine 3'5' cyclic-monophosphate (cAMP)-dependent protein kinase (PKA) overactivation contributes to hippocampal-dependent synaptic and cognitive deficits in exon-1 HD mice (110,139).

The PKA pathway is known to regulate specific types of long-term synaptic plasticity (reviewed in (255)), and to play a critical role in hippocampal-dependent learning and memory formation (256,257), but persistent and aberrant activation of PKA can lead to memory impairment (240,256,258-260). Likewise, increased hippocampal PKA activity leads to cognitive dysfunction in R6/2 mice as demonstrated by the beneficial effect of intra-hippocampal injection of Rp-cAMPs, a PKA inhibitor, on recognition memory (139). Reinforcing these findings, cAMP levels are higher in hippocampal nerve terminals from R6/1 mice than in controls, and dopamine type 1 (D1) and A2A receptors display increased response to their ligands in mutant mice. This leads to PKA overactivation in the hippocampus and participates in an occlusion mechanism (110). In fact, a combined chronic blockade of D1R and A2AR, but not a single acute or a chronic blockade of either receptor alone, normalizes PKA activity in the hippocampus and ameliorates cognitive dysfunction in R6/1 mice (110). Moreover, and in contrast to vehicle-injected mutant mice, R6/1 animals injected daily with SCH23390 (D1R antagonist) plus SCH58261 (A2AR antagonist) display a significant LTP induction *in vivo.* Overall these data show that D1R and A2AR blockade normalizes hippocampal PKA activity, enhances synaptic potentiation at the CA3-CA1 region and ameliorates cognitive dysfunction in R6/1 mice (110).

In HD, non-motor symptoms include sleep and circadian disturbances (reviewed in (261)). Interestingly, pathological up-regulation of cAMP/PKA signaling has been implicated in sleep and activity abnormalities in fly HD models. Elevated PKA activity in healthy flies produces patterns of sleep and activity similar to those found in flies expressing mutant huntingtin, whereas genetic reduction of PKA abolishes sleep/activity deficits, restores the homeostatic response and extends lifespan in HD flies. Remarkably, decreasing PKA also prevents immediate memory impairment in HD model flies (262).

Summing up, aberrant PKA activity may be a general consequence of mutant huntingtin expression, and may underlie neuronal dysfunction in distinct brain areas

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and several HD phenotypes. For instance, abnormalities in sleep and circadian rhythms have a negative impact on cognitive, emotional and psychiatric function.

Deficient cGMP signaling

The nitric oxide/soluble guanylyl cyclase/3',5'-cyclic guanosine monophosphate /cGMP-dependent protein kinase (NO/sGC/cGMP/cGK) signaling pathway has been widely implicated in synaptic plasticity, and in learning and memory in several brain regions, including the hippocampus (reviewed in (263)). Interestingly, neuronal NOS (nNOS) mRNA levels are decreased in the caudate of HD patients (264), and changes in nNOS protein levels also occur in the striatum and cortex of HD mouse models (265-269). The study of the integrity of the nNOS/cGMP pathway in the hippocampus of HD mice, and of its potential contribution to hippocampal learning and memory deficits, has shown that both nNOS and cGMP levels are significantly reduced in the hippocampus of R6/1 mice, and that an acute post-training injection with sildenafil, a selective inhibitor of the cGMP-specific phosphodiesterase (PDE) 5 (270), increases cGMP levels and improves novel object recognition memory and passive avoidance learning (271). These data support the idea that decreased hippocampal cGMP levels contribute to cognitive dysfunction in R6/1 mice. Another study performed in the rat 3-nitropropionic acid toxic model of HD shows that sildenafil treatment improves memory performance in the Morris water maze (272). Importantly, cGMP levels are also reduced in the hippocampus of HD patients (271). Thus, PDE5 inhibition may prove to be beneficial in ameliorating hippocampal-dependent cognitive deficits in HD.

Transcriptional dysregulation: CREB and its co-activator CBP

Transcriptional dysregulation has been shown in HD human brain, as well as in *in vivo* and *in vitro* disease models (241,273-278). Mutant huntingtin can cause transcriptional dysregulation by 1) sequestration of positive transcriptional regulators such as TATA-binding protein (279), specificity protein-1 (280) or cAMP-response element binding protein (CREB) binding protein (CBP) (279,281); 2) loss of interaction with negative transcriptional regulators, such as the repressor element-1 transcription/neuron restrictive silencer factor (NRSE), resulting in REST/NRSF complex nuclear translocation and transcriptional repression of several neuronal-specific genes (282); and 3)

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increasing ubiquitination and histone methylation, and reducing histone acetylation (283).

CREB is a transcription factor that mediates stimulus-dependent changes in the expression of genes critical for neuronal survival, plasticity and growth (284-287). CREB activity is regulated by phosphorylation at serine 133 (Ser133) and at additional sites, as well as by association with CREB co-activators (288). Indeed, CREB phosphorylation at Ser133 facilitates the binding of the transcriptional co-activator CBP (289-292). The interaction between CREB and CBP, or other members of the transcriptional machinery, facilitates gene expression (291,293). In fact, CBP has emerged as a key regulator of CREB-mediated transcription by acting as a CREB transcriptional co-activator (289,294,295) and as a histone acetyltransferase (HAT) to disrupt repressive chromatin structure and allow gene transcription (296-299). Expression of CREB-related target genes is downregulated in several *in vitro* and *in vivo* models of HD (197,300,301). Moreover, mutant huntingtin interacts with CBP and blocks its HAT activity (302). Importantly, hypoacetylation of histone H3 is associated with downregulation of genes in R6/2 mice and knock-in cell lines (303).

Activity-induced gene transcription is required for normal hippocampal synaptic plasticity and memory consolidation (47,304), and compelling evidence indicates that CREB is essential for activity-induced memory gene expression (305,306). Additionally, several studies show reduced chromatin acetylation and hippocampal LTP and long-term memory (LTM) deficits in mouse models with compromised CBP activity (307-312). In line with these data, CBP levels are reduced in the hippocampus of HD patients and Hdh$^{Q7/Q111}$ mice in close correlation with the presence of spatial and recognition memory deficits (150). Moreover, reduced CBP levels in Hdh$^{Q7/Q111}$ mice are associated with selective dysregulation of CREB/CBP-target genes related to memory and synaptic plasticity (*c-fos, Nr4a2 and Arc*) (150). Reduced CBP expression and/or activity have been associated with diminished H3 acetylation in mouse models of cognitive dysfunction (308,313,314). Consistently, decreased hippocampal CBP levels are paralleled by diminished H3 acetylation in Hdh$^{Q7/Q111}$ mice, suggesting that lower CBP levels and decreased histone acetylation are responsible, at least in part, for memory dysfunction in HD (150). In agreement with studies showing that CBP HAT activity plays a crucial role in memory consolidation processes (313), and that trichostatin A (TSA), a

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general histone deacetylase inhibitor, enhances hippocampal-dependent memory consolidation by increasing the expression of specific genes during memory consolidation (315), TSA reverses LTM impairment in Hdh$^{Q7/Q111}$ mice, accompanied by increased levels of *c-fos* and *Arc* (150).

Therapeutic strategies

Currently, there is no known effective treatment for cognitive dysfunction in HD as so far clinical trials have tested traditional cognitive enhancers and anti-depressants without signs of efficacy (reviewed in (316)).

The fact that in HD neuronal death does not occur until late stages of the disease suggests that neuronal dysfunction and abnormal synaptic plasticity occur earlier and are responsible for cognitive decline, which opens a window for therapeutic interventions. Moreover, targeting those early pathophysiological events is likely to provide better therapeutic outcomes than trying to prevent cell death once neurons are severely affected. As explained above, the presence of mutant huntingtin alters distinct cellular and molecular mechanisms, all of which can directly or indirectly impact on neuronal functioning, leading to synaptic and cognitive impairment. In this line, several genetic, pharmacological and non-pharmacological approaches have proved beneficial in HD models, not necessarily because they specifically target an altered mechanism or signaling cascade that participates in neuronal dysfunction leading to cognitive impairment, but because they improve the expression of receptor subunits, neurotrophic factors or other molecules involved in plasticity processes, and/or because they reduce the level of detrimental effectors. Next, we provide one such example. PDEs are the enzymes responsible for cAMP/cGMP degradation that through their different subcellular distribution allow compartmentalization and tight temporal and spatial control of cyclic nucleotide signaling (317). PDE inhibitors are increasingly being considered as cognitive enhancers (318-321), and the cognitive-enhancing properties of a PDE10A inhibitor were recently examined in R6/1 mice. PDE10A, a cAMP/cGMP dual-substrate PDE, is enriched in nuclear fractions both in wild-type and R6/1 mouse hippocampus, without differences in its levels or intracellular distribution between genotypes. Chronic treatment with papaverine, a PDE10A inhibitor, improves spatial and object recognition memory in R6/1 mice, and

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likely works through the activation of the PKA pathway, as the phosphorylation level of distinct cGK substrates is not modified in either genotype (322). These results appear to contradict the finding that increased PKA signaling in R6 mice hippocampus leads to hyperphosphorylation of PKA membrane targets implicated in synaptic plasticity and learning and memory, and to impairment of object recognition and spatial memory (139), while targeting aberrant PKA signaling improves hippocampal-dependent synaptic and cognitive function (110,139). Overall, these studies support the idea that hyperactivity of hippocampal PKA in HD mice is not a global event, but rather restricted to specific subcellular domains (139,322). In fact, the memory-enhancing effect of papaverine in R6/1 mice likely involves a partial, but significant, recovery of GluA1 phosphorylation levels together with increased CREB phosphorylation in the hippocampus (322). Thus, PDE10 might be a good therapeutic target to improve hippocampal cognitive impairment in HD. Remarkably, although striatal PDE10A levels are reduced well before motor symptom onset in HD (323), as confirmed by a study with the radioligand [18F] MNI-659A (324), PDE10 is being targeted for striatal dysfunction. Indeed, PDE10A inhibitors have attracted interest as potential novel pharmacotherapies for HD (325-329), with ongoing clinical trials (329). Nevertheless, in this section we chose to focus on those strategies with therapeutic potential for treating cognitive dysfunction in HD whose choice is justified by the identification of an affected pathway.

Functional and morphological changes in the neocortex have been proposed as initial triggers of striatal pathology in HD. In this context, there is an early and specific reduction in cortical Kalirin-7 levels in HD mice, paralleled by early cortical dendritic spine alteration, impaired corticostriatal LTP and cognitive deficits (136). It is noteworthy that the number of cortical glutamatergic synapses in cultured HD neurons can be restored upon Kalirin-7 overexpression (136). Although the study of the impact of Kalirin-7 overexpression in adult HD mice is hampered by methodological limitations, the early loss of Kalirin-7 could contribute not only to decreased spine density, but probably also to altered corticostriatal synaptic transmission and cognitive deficits. In summary, the identification of Kalirin-7 downregulation at early HD stages and its role in modulating HD cortical excitatory synapses (136) allows us to hypothesize that cortical function could be restored by increasing the levels of Kalirin-

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7. Such increase could be the first step to prevent subsequent loss of corticostriatal connectivity, striatal dysfunction and, later, striatal neuronal degeneration.

Concerning spine loss in MSNs, two mechanisms have been elucidated. One involves aberrant reactivation of juvenile GluN3A subunits, which promotes early and progressive dendritic spine pathology that likely underlies cognitive and motor impairment, and ultimately, neuronal death. In fact, lack of GluN3A ameliorates striatum-dependent cognitive and motor decline, and reduces striatal cell death in YAC128 mice (130), which has led to the proposal that GluN3A might be a good target for therapeutic approaches in HD (325). The other mechanism is associated with dysregulation of intracellular neuronal Ca^{2+} signaling, as enhanced nSOC has been shown to cause synaptic loss in HD MSNs (131). Interestingly, inhibition of nSOC with EVP4593 not only prevents spine loss in YAC128 MSNs, *in vitro* and *in vivo* (131), but also protects cultured HD MSNs against glutamate toxicity and improves motor symptoms in a fly model of HD (195), thus supporting the possibility that targeting nSOC could have a beneficial impact on HD.

Another crucial regulator of synaptic plasticity and neuronal survival proposed as an excellent therapeutic target for treating the clinical hallmarks of HD is BDNF (164,165,330). However, BDNF administration has shown important methodological drawbacks in HD models (200), and several studies indicate that increasing BDNF levels only partially improves HD phenotype (129,141,331-333). Previous studies conducted by our group and others demonstrate reduced TrkB levels in patients and in different HD models (218-220). Together with the emerging evidence of imbalanced TrkB and p75[NTR] expression/signaling in HD (135,201,220,221), this could contribute to the incomplete reversion of HD pathology by the administration of the neurotrophin.

Although a general genetic reduction of p75[NTR] levels in Hdh[Q7/Q111] mouse brain does not prevent motor learning deficits or corticostriatal LTP abnormalities, the levels of DARPP-32, a striatal marker known to be reduced in HD mice from early stages (334), are reestablished (135). These results suggest that striatal neuronal dysfunction can be slightly ameliorated, but not prevented, by downregulation of aberrant p75[NTR] expression in Hdh[Q7/Q111] brain. On the other hand, specific knockdown of striatal p75[NTR] reverses corticostriatal LTP abnormalities in BACHD mice (201). In this context, it is important to note that p75[NTR] levels are not altered in the cerebral cortex of HD

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mice and patients (135,221), suggesting that decreased cortical p75^{NTR} levels in HD mice can be deleterious for synaptic plasticity and cognitive processes. Altered expression of TrkB and p75^{NTR} receptors disturbs BDNF-induced neuronal protection in a cellular HD model, and reduction of p75^{NTR} levels in corticostriatal slices of Hdh$^{Q111/Q111}$ mice not only increases cell survival, but also prevents the cell death induced by BDNF (221). Therefore, targeting p75^{NTR} has the potential to improve corticostriatal plasticity and reduce cell death in HD.

Besides impairment in corticostriatal connectivity, disturbances in hippocampal function contribute to HD memory deficits in middle disease stages. Thus, hippocampal dysfunction is an important hallmark of HD pathology, and preservation/restoration of hippocampal function could represent a promising alternative strategy to prevent memory loss in HD. In line with recent studies supporting a critical role for p75^{NTR} in hippocampal-dependent synaptic plasticity (223,224), normalization of hippocampal p75^{NTR} levels in distinct HD mouse models with genetic or pharmacological approaches rescues hippocampal synaptic plasticity, memory deficits and dendritic spine alterations, likely by normalization of the RhoA GTPase activity (107,135). Overall, this evidence suggests that antagonism of p75^{NTR} could represent an excellent approach to restoring BDNF-mediated signaling in HD corticostriatal pathway, thereby restoring corticostriatal connectivity (201), ameliorating hippocampal synaptic dysfunction and memory deficits (135) and improving cell survival (221). An important consequence of these findings is that whereas TrkB is widely and robustly expressed in the adult brain, p75^{NTR} has a restricted tissue distribution, and its expression is developmentally downregulated in most parts of the brain, which makes the targeting of p75^{NTR} likely to have fewer side effects in HD patients. Remarkably, chronic administration of fingolimod (FTY720), an immunomodulatory drug used in the treatment of multiple sclerosis patients (335), ameliorates LTM deficits and dendritic spine loss in CA1 hippocampal neurons from R6/1 mice, and these effects are accompanied by normalization of p75^{NTR} levels and reduced astrogliosis in the hippocampus (107). Interestingly, chronic administration of FTY720 improves motor function, prolongs survival and reduces brain atrophy in R6/2 mice, and these effects are accompanied by increased BDNF levels, strengthening of neuronal activity and connectivity, reduction of mutant huntingtin aggregates and

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increased phosphorylation of mutant huntingtin in residues predicted to attenuate its toxicity (336). It would be useful to evaluate whether the normalization of p75^{NTR} levels and reduction of astrogliosis reported in the hippocampus of FTY720-treated R6/1 mice (107) also occur in the striatum.

Aberrant PKA signaling promotes hippocampal-dependent synaptic and memory impairment in HD mice (110,139). Notably, abnormal PKA signaling is also responsible for sleep disturbances in fly HD models, leading to the proposal of sleep and cAMP/PKA as prodromal indicators of disease, and therapeutic targets for intervention (262). Increased signaling through D1R and A2AR contributes to PKA overactivation and hippocampal-dependent synaptic and memory impairment in HD mice (110). Based on the finding that PKA activity is also increased in the hippocampus of HD patients (139), we propose that targeting D1R and A2AR might be a therapeutic approach to improve hippocampal-dependent cognitive function in HD. The combined antagonism of the two receptors normalizes striatal PKA activity, but does not ameliorate motor deficits (110), and inactivation of A2AR prevents working memory deficits in R6/2 mice, but does not modify motor dysfunction either (233). Actually, although striatal A2AR emerges as a novel target to fight against cognitive inflexibility, namely working memory impairment (233), this exciting therapeutic possibility needs to be carefully considered since targeting A2AR for HD motor symptoms remains largely controversial. Some studies demonstrate a neuroprotective effect of an A2AR antagonist in toxic models of HD, while others report no recovery from motor deficits or a delayed deterioration of motor performance after treatment with A2AR agonists in R6/2 mice (reviewed in (337-339)). Thus, targeting A2AR in HD is a puzzling issue, and the therapeutic window for A2AR antagonists might be restricted to the early phases of HD. Conversely, activation of A2AR normalizes synaptic activity in the striatum of symptomatic R6/2 mice, and may thus help to restore corticostriatal connectivity at later stages of the disease (232).

In contrast to cAMP levels (110), hippocampal cGMP levels are reduced in HD mice (271). Since targeting the cGMP-specific PDE5 improves cGMP levels and ameliorates hippocampal-dependent learning and memory in R6/1 mice, and cGMP levels are also diminished in the hippocampus of HD patients (271), normalization of cGMP levels emerges as an approach to counteract deficits in hippocampal cognitive function in

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HD. Given that the nNOS pathway is highly affected in the striatum and cortex too (265-269), it is tempting to speculate that targeting this pathway might also ameliorate corticostriatal dysfunction. So far, two studies have shown that the PDE5 inhibitor sildenafil protects against biochemical and behavioral abnormalities in the 3-nitropropionic acid toxic model of HD (272,340), but whether sildenafil or other PDE5 inhibitors improve corticostriatal connectivity, corticostriatal-dependent learning and/or motor dysfunction in genetic models of the disease remains to be addressed. It is noteworthy that cGMP can promote mitochondrial biogenesis and ATP synthesis (341), which is relevant because mitochondrial function is known to be compromised in HD (342). Furthermore, PDE5 inhibitors have emerged as a potential therapeutic strategy to improve not only cognitive function, but also to target neuroinflammation and neurodegeneration (reviewed in (343)), and thus they could be valuable multi-purpose drugs in the context of HD. Moreover, it is expected that the use of PDE5 inhibitors will prove to be of therapeutic interest because under physiological conditions transient elevations in striatal intracellular cGMP levels increase neuronal excitability and facilitate spontaneous and evoked corticostriatal transmission (344), which would improve connectivity in HD. Interestingly, intrastriatal infusion or systemic administration of the selective PDE10A inhibitor TP-10 increases the responsiveness of striatal MSNs to cortical input (345), and this effect depends on the NO-sGC-cGMP signaling cascade (346). Considering these findings and the reports on reduced nNOS mRNA in postmortem tissue from HD subjects (264) and in HD mouse models (265,269), it is likely that a combination of both PDE10A inhibitors and sGC activators will be useful to improve corticostriatal transmission in HD.

As an alternative, or complementary, strategy to restore hippocampal function in HD at middle and advanced disease stages, we propose the modulation of CBP levels and/or activity. CBP levels are reduced in the hippocampus of Hdh$^{Q7/Q111}$ mice, where they are accompanied by diminished histone 3 acetylation and spatial and recognition memory deficits (150). Since treatment with a general HDAC inhibitor reverses LTM impairment in Hdh$^{Q7/Q111}$ mice, CBP loss of function may result in decreased memory-related gene transcription and be responsible, at least in part, for the spatial and recognition memory deficits observed in Hdh$^{Q7/Q111}$ mice (150). Remarkably, several studies suggest an important role of CBP loss of function in polyQ-dependent striatal

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neurodegeneration in HD models (265,300,347-349). It is noteworthy that restoration of CBP striatal function by overexpression of CBP or by using HDAC inhibitors improves striatal atrophy and survival, as well as motor symptoms in HD models (350,351). Therefore, therapies aimed at increasing CBP levels and/or activity by using HDAC inhibitors hold the promise to be a good approach to prevent corticostriatal- and hippocampal-dependent dysfunction, motor symptoms and, ultimately, neurodegeneration. Remarkably, recent studies have found that HDACi 4b, a HDAC1/3 inhibitor, has beneficial transgenerational effects in HD mice through altered DNA and histone methylation (352), while RGFP966, an inhibitor of HDAC3, improves motor deficits on rotarod and open field, accompanied by neuroprotective effects on striatal volume and decreased glial fibrillary acidic protein immunoreactivity in the striatum of N171-82Q mice (353). Therapies targeting transcriptional dysregulation in HD include sodium phenylbutyrate (phase I) and HDACi 4b (preclinical) (354). Even though research in this area is still at a preliminary stage, and crucial issues need to be addressed, such as the development of new potent and more selective HDAC inhibitors, with excellent blood-brain-barrier permeability, less cytotoxicity and reduced side effects, HDAC inhibitors show promise as a new avenue for therapeutic interventions in HD.

Concluding remarks

In summary, we have reviewed new evidence for early cortical and corticostriatal dysfunction in HD followed by hippocampal dysfunction, prior to the manifestation of motor symptoms, driving the search for novel therapeutic approaches to improve HD pathology at different disease stages. In particular, we propose that a first therapeutic intervention has to be focused on preserving/restoring corticostriatal connectivity, which would impact on intrinsic striatal function. In this context, given that reduced levels of Kalirin-7 are responsible, at least in part, for the early altered corticostriatal function, we propose the preservation/restoration of Kalirin-7 levels as an early therapeutic intervention to maintain functional cortical excitatory synapses. In the case of MSNs, recent evidence indicates that spine loss in YAC128 neurons is associated with reactivation of juvenile GluN3A. Although the downstream events are not fully characterized, these findings support the development of GluN3A-selective

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antagonists and/or alternative therapeutic approaches to block abnormal GluN3A expression. Aberrant InsP3R1 activity leading to reduced ER Ca^{2+} levels and increased spine SOC are also implicated in MSNs spine loss, suggesting that targeting nSOC in MSNs might prove to be useful. Targeting the PKA pathway may ameliorate hippocampal plasticity and cognitive function in HD. To improve not only corticostriatal dysfunction, but also hippocampal-dependent deficits in HD, we propose 1) genetic or pharmacological inhibition of p75^{NTR} to preserve synaptic plasticity and cognitive function, as well as prevent striatal neuronal death, and 2) treatment with HDAC inhibitors that exhibit promising therapeutic effects in restoring memory and improving striatal survival and motor coordination at more advanced disease stages. Data obtained so far indicate that inhibition of PDE5 ameliorates hippocampal-dependent learning and memory, but further studies are needed to address the therapeutic potential of targeting cGMP signaling using PDE inhibitors to improve corticostriatal dysfunction in HD. The use of PDE10A inhibitors will likely prove to be beneficial by improving both hippocampal and corticostriatal deficits in HD.

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Table 1. Genetically modified HD mouse models.

Mouse model	Construct	Promoter	CAG repeat size	Lifespan	References
R6/1	Insertion of the exon 1 of human *HD* gene into mouse genome	Human huntingtin	116	32-40 w	(12, 77-79)
R6/2	Insertion of the exon 1 of human *HD* gene into mouse genome	Human huntingtin	144	13-16 w	(12, 77-80)
N171-82Q	Insertion of the first 171 aa from the N-terminal fragment of the human *HD* gene into mouse genome	Mouse prion protein	82	16-24 w	(81)
HD94- tet off	Insertion of a chimeric mouse/human exon 1 fragment with polyQ expansion into mouse genome	CamKIIa-tTA	94	Normal	(82)
YAC72	Yeast artificial chromosome expressing full-length human mutant huntingtin	Human huntingtin	72	Normal	(83-85)
YAC128	Yeast artificial chromosome expressing full-length human mutant huntingtin	Human huntingtin	128	Normal	(86-90)
BACHD	Bacterial artificial chromosome expressing full-length human mutant huntingtin	Human huntingtin	97 CAG/CAA mixed repeats	Normal	(76, 87, 91, 92)
Hdh92Q	Replacing exon 1 of the mouse *huntingtin* gene with a mutant human exon 1	Mouse huntingtin	92	Normal	(93-95)
Hdh111Q	Replacing exon 1 of the mouse *huntingtin* gene with a mutant	Mouse huntingtin	111	Normal	(94-97)

		human exon 1			
CAG140	Inserting CAG repeats into the mouse *huntingtin* gene	Mouse huntingtin	140	Normal	(98)
CAG150	Inserting CAG repeats into the mouse *huntingtin* gene	Mouse huntingtin	150	Normal	(99-101)

Information about construct insertion, the promoter used to express the mutation, the CAG repeat number and the lifespan. Weeks (w).

Table 2. Alterations in synaptic plasticity in HD mouse models.

Mouse model	Cerebral cortex	Striatum	Hippocampus	References
R6/1	Loss of cortical plasticity (8-10 w) Increased LTD (2 mo) followed by a reduction in LTD expression (5 mo) and loss of LTD (7-9 mo) at perirhinal synapses Decreased dendritic spine density and spine length (8 mo)	Decreased spontaneous EPSCs in MSNs (9-13 mo) Increased spontaneous IPSCs (12-15 mo) Decreased dendritic spine density and spine length (8 mo)	Decreased LTP in brain slices (5 w) Impaired LTP *in vivo* (13-14 w) Increased LTD at CA1 synapses (12 w) Decreased dendritic spine density (20 w)	(102-112)
R6/2	Hyperexcitable cortex and greater susceptibility to seizures (3 w) Increased spontaneous IPSCs (3-4 w) Decreased spontaneous IPSCs and increased spontaneous EPSCs (13 w) Dendritic spine loss (3-4 w) Dysfunctional communication between cortex and striatum (7-9 w)	Progressive decrease in spontaneous EPSCs in MSNs (5-7 w) No differences in the LF IPSCs Increased spontaneous IPSCs (5-7 w and 9-14 w) Progressive dendritic spine loss (4-10 w)	Reduced LTP and aberrant LTD at CA1 synapses (5 w)	(67, 104, 113-123)
YAC72	Increased NMDAR-mediated EPSCs in MSNs (21-31 d) after stimulation of cortical afferents in corticostriatal slices Altered early corticostriatal synaptic function (21-30 d), including presynaptic dysfunction and propensity towards synaptic depression		Increased LTP (6 mo) Reduced LTP (10 mo)	(83, 124-126)
YAC128	Altered early corticostriatal synaptic function (21-30 d) Presynaptic dysfunction, propensity towards synaptic depression and altered AMPAR function Biphasic age-dependent changes in		Reduced paired-pulse depression in the DG (3-6 mo) Enhanced post-tetanic and short-term potentiation	(104, 115, 127-131)

	corticostriatal function: Increased synaptic currents and glutamate release (1 mo) Reduced evoked synaptic currents and glutamate release (7-12 mo)		after HF stimulation (3-6 mo)	
	Increased spontaneous EPSCs (12 mo) Increase spontaneous IPSCs (6 and 12 mo)	Reduced spontaneous EPSCs (6 and 12 mo) Reduced spontaneous LF IPSCs (6 and 12 mo) Increased spontaneous HF IPSCs (1, 2, 12 mo) Progressive dendritic spine density loss (3, 6, 12 mo)		
BACHD	Progressive reduction of cortical excitation and inhibition of layer 2/3 pyramidal cells (3-6 mo)	Progressive reduction of excitation onto MSNs (3-6 mo) High excitability of MSNs (18 mo) Reduced dendritic spine density (18 mo)	n.r.	(87, 91, 92, 132, 133)
Hdh92Q	n.r.	n.r.	Reduced LTP (4-6 mo)	(134)
Hdh111Q	n.r.	n.r.	Reduced LTP (2 mo) Reduced actin polymerization in dendritic spines after TBS-induced LTP	(134)
Hdh 7Q/111Q	Impaired induction and maintenance of corticostriatal LTP (2 and 4 mo)		Reduced LTP (6 mo) Decreased dendritic spine density and altered distribution with a specific reduction in the	(135, 136)

		proportion of thin spines (8 mo)		
	Decreased dendritic spine density and a shift in their distribution (2 mo)	No alterations in dendritic spine density (2 mo)		
	Progressive decrease of glutamatergic excitatory postsynaptic sites (2 and 8 mo)	Decrease of glutamatergic excitatory postsynaptic sites (8 mo)		
CAG140	Increased spontaneous EPSCs (12 mo) Increased spontaneous IPSCs (6 and 12 mo)	Reduced spontaneous EPSCs (12 and 18 mo) Reduced spontaneous LF IPSCS (12 and 18 mo) Increased spontaneous HF IPSCs (12 mo) Reduced thalamostriatal axondendritic terminals (1 mo) Loss of corticostriatal terminals (12 mo) Reduced dendritic spines in MSNs (20-26 mo)	n.r.	(104, 115, 137, 138)

Alterations in synaptic plasticity (electrophysiological properties and dendritic spine density/morphology) of neuronal populations from the cerebral cortex, striatum and hippocampus of HD mouse models. Long-term depression (LTD); Long-term potentiation (LTP); Excitatory postsynaptic currents (EPSCs); Inhibitory postsynaptic currents (IPSCs); *Cornus Ammonis* 1 (CA1); Medium-sized spiny neurons (MSNs); N-methyl-D-aspartate receptor (NMDAR); α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor (AMPAR); Dentate gyrus (DG); low frequency (LF); high frequency (HF); Theta burst stimulation (TBS); Weeks (w); Months (mo); Not reported (n.r.).

Table 3. Cognitive, psychiatric and motor deficits in HD mouse models.

Mouse model	Cognitive and psychiatric deficits	Motor deficits	References
R6/1	8-12 w	14 w 8 w (AR)	(79, 102, 106, 136, 139)
R6/2	4-8 w	6-8 w	(79, 120, 140-142)
N171-82Q	14 w	11 w	(81, 143, 144)
HD94- tet off	n.r.	4 w	(82, 145)
YAC72	n.r.	Hyperactivity (7-9 mo) 16 mo	(83)
YAC128	7-8.5 mo	Hyperkinesia (3 mo) Hypokinesia (6 mo) 2-12 mo (AR)	(87, 88, 90, 146, 147)
BACHD	2-12 mo	2-12 mo (AR)	(76, 87, 91, 92)
Hdh92Q	4 mo	21 mo	(148, 149)
Hdh111Q	n.r.	24 mo	(96)
Hdh7Q/111Q	6 mo	8 mo 2-6 mo (AR)	(135, 136, 150-152)
CAG140	4-6 mo	Hyperkinesia (1-3 mo) Hypokinesia (from 3 mo) 4-12 mo	(98, 153)
CAG150	4 mo	4-10 mo	(100, 154)

Information about the age at which HD models start to exhibit cognitive, psychiatric and motor deficits. Motor deficits include several parameters: 1) learning of new motor skills (evaluated with the accelerating rotarod (AR) task), 2) hypo/hyperactivity, and 3) motor coordination (evaluated using several motor tests). Specific information about each model can be found in the cited references. Weeks (w); Months (mo); Not reported (n.r.).